

What Future for Higher Education?

THE conference on higher education in Cambridge last week (see page 159) has helped to clarify some of the issues that have perplexed higher education in Britain for the past two years. It has also unfortunately emphasized yet again that it will be a long time before acceptable solutions are agreed upon. A part of the trouble is that the change of governments in Britain has made it necessary to tread over familiar ground a second time, but it is also clear that academics of all kinds, not simply university teachers, are far from clear about the directions in which they would like to see progress made. In the middle distance, this is the most serious obstacle to the change now plainly necessary. Further away, however, it is also clear that the users of the higher education system, not merely the students and the potential students but their potential employers, will have to make up their minds on several important issues, the extent to which vocational training should play a part in higher education and the importance of non-industrial occupations such as social work in the future pattern of employment included. When so many uncertainties abound, the biggest danger is that the will to change will somehow be paralysed.

It is therefore important to remember that somehow, willynilly, there has grown up a common understanding that higher education in Britain will have to grow until between 800,000 and 1,000,000 places are available in all kinds of institutions. There seems to be a momentum in the system which transcends analysis, and which has already carried the growth of the higher education system far beyond the recommendations of the Robbins commission less than ten years ago. Then, in 1963, it was argued that the number of places in higher education necessary to satisfy the needs of properly qualified students should be 305,000 by the autumn of 1971, but now it seems likely that there will be more than 430,000 students in higher education by October, roughly half of them at universities. Ten years from now, when Robbins asked that there should be more than half a million places, recent tendencies suggest that there will be room for 727,000 students. To be sure, it is always possible that this tendency to growth could be truncated or at least postponed by sufficiently energetic restrictions on public expenditure, but there is no real prospect that the demand for higher education can be made to go away. By the end of the century, higher education of one kind or another is likely to become a part of most young people's development. For practical people, the question is to know how to make this prospect easily come true.

Money is evidently a critical consideration. On the face of things, the growth now planned for higher education as a whole implies a corresponding increase of cost. If the present cost of higher education is 1.5 per cent of the Gross National Product, is it not likely to cost 3 per cent of the GNP when the system as a whole has doubled yet again? And is it not improbable that governments cast in the vein of recent British governments will decline to foot such a seemingly extravagant bill? Luckily, in the years immediately ahead at least, this dilemma may not be forced upon the Treasury. For one thing, there

are probably important savings to be made by the fuller use of expensive capital facilities on which much of the expenditure of recent years has gone. Second, there are likely to be significant if marginal economies in the use of some of the new techniques of educational technology. Third, it now seems probable that public expenditure on research will for practical purposes mark time as the university sector grows in numbers (which is something to be worried about separately). Those who believe that the government may have no cause for turning nastily against the universities and the other components of the higher education system in the next few years may be a little optimistic, but the real money problems are for the eighties, not the decade immediately ahead. By then, the structure of British higher education may be—certainly it should be—quite different from what it is at present.

The separation between the different kinds of establishments of higher education is one of the most serious defects of the present system. The conference in Cambridge last week showed very little evidence that these institutions will find a better way of living peaceably cheek by jowl. After a shaky beginning, the polytechnics now seem well set as alternatives to the universities with curricula which differ more in character than in difficulty. For some years at least, the chances are that both types of institution will relish the separateness. In time, no doubt, many polytechnics will seem as places of higher education to be better than some universities, thus demonstrating what everybody knows—that the quality of an institution is a function of the quality of its teachers and not the character of its constitution. The prospect of such a happy outcome should not, however, conceal the absurdity which now consists in the separate arrangements for entry to universities and to polytechnics. For many young people leaving school, the first objective is to find a place at a university and only when such an ambition is frustrated is a hunt made through the lists of polytechnics with vacancies to fill. So long as such a system persists, the traditional snobbery of British education will divide the polytechnics from the universities. But a still more serious problem is that the colleges of education, at present housing 27 per cent of all students in higher education, are acknowledged to be institutions too severely limited to a single purpose of training teachers. The introduction of the BEd degree for those intending to teach in secondary schools has smoothed some previously ruffled feathers but has also served to exaggerate the differences between primary and secondary teachers. There is some merit in the proposal for broadening the scope of colleges of education, sometimes by the grafting on of nursing training, but it would be much better for everybody concerned if the colleges were made a regular part of a unitary system of higher education. Can such a step be long delayed?

For the universities, the pattern of growth which is now in prospect is bound to bring important changes in the character of academic life. For one thing, whether or not research funds are relatively diminished, it is inevitable that the new circumstances will require more concern



among academics for the quality of teaching. The increasing diversity of the interests of the student body as well as the growth of numbers will require as much. One of the cheerful developments in recent months is, luckily, the willingness of academics to give teaching the status which it deserves—a point faithfully reflected at the conference last week. But how easy will it be to recruit young people to the university faculties if they are given to understand that research may not indefinitely be an indispensable part of their work? Alternatively, how easy will it be to ensure that when there are more teachers and fewer researchers, what money there is finds its way into the hands of those most likely to spend it well, not necessarily the heads of university departments? These are obviously important matters in which (in British circumstances) the research councils have important parts to play. It is only natural to expect that, in circumstances like these, there will be a tendency for research appointments unaccompanied by teaching duties to be fewer and growing pressures to insist that academic research carried out away from universities should be more closely linked with the academic world. Because the next two years are likely to see the makings of this new balance between teaching and research, these problems are likely to seem to many academics to be the most immediate consequences of growth in higher education.

With all this change, the pattern of undergraduate education is certain to be transformed. The question still to be decided is whether the change will be liberal or reactionary. On the one hand, there are powerful arguments in favour of a more liberal start to undergraduate education at the universities, partly so as to provide a better foundation for specialized or vocational studies coming later and partly so as to make less sharp the need to choose between one course of specialist studies and another. Among university scientists at Cambridge last week, some development along these lines seems to have been considered inevitable. The difficulty is to know what form a more liberal undergraduate curriculum should take. There is much to be said for the simple abolition of undergraduate courses in subjects too narrow to be taught with integrity. Evidently undergraduate courses in microbiology are to be deplored on educational grounds. So too are biochemistry and even metallurgy. There is also much to be said for the several proposals recently put forward to show how undergraduate teaching might consist of a period of more general study followed by a period of special or vocational study. Professor A. B. Pippard's scheme for two years of general work (with some specialism on the side for those who want it) leading to a degree has been usually attacked for the wrong reasons. The truth is that some device like this, that will allow young people an opportunity to use the first university degree as a stepping stone to something qualitatively different, is essential if some means of satisfying the volatile and unpredictable demands of the labour market is to be found. But that is only one of the many reasons why the Pippard proposals deserve serious attention.

Universities are at least prepared to worry about the curriculum. Other parts of the education system are for the time being too complacent. One of the most serious problems in modern Britain is, however, the shortage of specialized teachers and the inadequacy of the training of those who can be tempted into schools. Other kinds of vocational training, from medicine to technology, are similarly skimmed in breadth. For the time being, it is

assumed that the coexistence of, for example, the polytechnics and the universities is to be taken as a proof that two quite different kinds of curricula are necessary. But may it not in practice be important to broaden the foundations of all vocational education, not merely those forms of it traditionally associated with the universities? And in circumstances like that, will it not be found that the pattern of teaching in the polytechnics (or the colleges of education) will become more like each other than they seem at present?

The catalogue of problems in higher education is so easily extended that it may seem forbidding to many of those most intimately involved. It is therefore important that the difficulties now coming to the surface are largely the products of the entirely welcome growth of the system of higher education and of the recognition that the time has come to weld several separate parts into a more cohesive whole. Given the willingness of governments to foot reasonable bills, the process of change could be not merely painless but constructive. It is, however, important that the system of higher education as a whole should somehow be capable of defending itself against the outside world and especially from the niggardliness of governments. This is one of the reasons why universities would be well advised as quickly as possible to sacrifice some of their present individual autonomy for the sake of a more powerful outward stance; it is better to make rational arrangements for the division of labour among the universities than to have these imposed from outside. Similarly, it would be better for the universities, the polytechnics and the colleges of education to define their common interests in a situation in which each of them is separately financed, than to find themselves separately at the mercy of public authorities who fail to appreciate what Sir Eric Ashby calls their inner logic.

100 Years Ago



WE quote the following pleasant "international" from the *New York Technologist*:—In view of recent remarks concerning the action of the British Government in regard to the expedition proposed by British scientific men, for the purpose of observing the approaching eclipse, it is but justice to say that on proper representation being made to Mr. Lowe, the Chancellor of the Exchequer at once expressed his opinion that such an expedition was one eminently worthy of government aid, and perfect arrangements as regards ships, funds, &c., have been made. One good result has, however, attended this delay on the part of the British Government—it has afforded an opportunity for the exchange of very pleasant courtesies between the scientific men of the United States and those of Great Britain. As soon as Prof. Peirce heard that their government had refused the use of the necessary ships, he at once tendered to the English scientists all the facilities at his command; and they were ample. No one doubts that, under similar but opposite circumstances, the same offer would have come from the other side; for, however stubbornly *Alabama* controversies may hold out, science takes no cognizance of them."

From *Nature*, 3, 232, January 19, 1871.

OLD WORLD

TELESCOPES

How Pilot Works

by our Astronomy Correspondent

BEHIND the closed doors of the council chamber at Burlington House and in the Athenaeum afterwards, the Royal Astronomical Society has always been interested in the management of British astronomy. But lately, under the presidency of Sir Bernard Lovell, some of the concern is becoming perceptible to the society's membership. Last Friday all of the ordinary meeting of the society was devoted to a discussion of the instruments that are being developed for the Anglo-Australian telescope under the guidance of the SRC. To some extent, this is a controversial topic because several astronomers are worried that some important instruments will not be ready in time.

The meeting was neatly timed because that day and the preceding Thursday there had been a meeting of the SRC Panel for the Instrumentation of Large Optical Telescopes—known as the PILOT panel—that was set up in 1968 at the instigation of Mr J. F. Hosie of the SRC, director of the astronomy, space and radio board. The establishment of the panel may have been a reaction to the situation which occurred after the completion of the 98-inch Isaac Newton Telescope at Herstmonceux when several important pieces of equipment were not ready for astronomers to use—a situation described as a catastrophe by one astronomer who says that the mistake was in not involving some of the younger people in the planning of the telescope. In any case, it seems to have been wise of Mr Hosie to apply an age limit of forty on the panel at least in principle, although with the passage of time that boundary condition seems to be breaking.

According to the present chairman of PILOT, Professor J. Ring of Imperial College, the panel considers its functions to be to accept direct responsibility for designing particular instruments, and to consider whether proposals submitted to the SRC from astronomers working in the universities fit into the general scheme. A corollary is that the panel is looking for gaps in the instrumentation available in Britain and abroad that need to be filled. Instruments being prepared under the auspices of the panel for the Anglo-Australian telescope are divided into two classes—what are termed “people’s” instruments available for communal use, and more sophisticated instruments that would only be used by a few astronomers.

Last Friday, the PILOT panel had

been discussing a design study for the control system of the Anglo-Australian telescope, which was described to the meeting by Dr V. C. Reddish of the Royal Observatory, Edinburgh. The rationale behind the expense of a sophisticated control system is to reduce the wasted time between observations when the telescope shutter is closed while the telescope is being directed to the next observation. According to Dr Reddish this sometimes amounts to 50 per cent of the operating time. Experience with the 200-inch Hale telescope and at Edinburgh suggests that there could be a 50 per cent increase in efficiency by means of a computer controlled system allowing the astronomer to feed in information for the next observation while the telescope shutter is open and an observation is being made. Dr Reddish said that in the design study it is envisaged that the telescope would be more efficiently and more accurately controlled than present telescopes.

Mr Hosie said at the meeting that the construction of the 150-inch telescope was going well, but agreed that the PILOT panel was anxious about the possibility of some of the equipment not being ready on time. It is now expected that the first allocations of time on the telescope will be made at the end of 1974—the construction of the telescope had been put back six months by the death of the first project manager, Mike Jeffries, who by all accounts had been doing a fine job. The telescope is now going to cost more than was estimated in 1966–67, and the total capital cost to be shared between the two countries will now be A\$13 million. Although approval for the additional cost has been obtained there are still problems—Mr Hosie said that if the astronomers and designers get all that they are at present asking for, still more money will be needed. He was asking people to think in terms of simple equipment that could be upgraded in the future when more money will be available.

SCHIZOPHRENIA

Promising New Drug

A new drug for long-term treatment of schizophrenia seems to offer several advantages over preparations now widely in use. Unveiled at a press conference in London last week, the drug, which goes under the trade name of Orap, is claimed to be a specific antipsychotic which does not produce many of the adverse side reactions that have dogged long-term treatment of schizophrenia in the past few years. If these claims are substantiated the new drug will be a boon to patients who are being treated outside hospital for a

disease which has a particularly high relapse rate.

One of the chief problems with long-term management of schizophrenia is that the most popular tranquilizers, while very effective for treating the acute phase of the disease, tend to cause drowsiness or Parkinsonism if they are administered over long periods. These side-effects present difficulties for patients who are trying to carry out normal occupations, and it is a chief factor in the high relapse rate for the disease. More than half of the patients discharged from hospital are eventually readmitted for further treatment.

Orap adds a third class of drug to these now being used. It is a primozide—a diphenylbutapiperidine—while the others are either phenothiazines such as chlorpromazine or butyrophenones such as haloperidol. The manufacturers, Janssen Pharmaceuticals Ltd, claim that the drug has acquitted itself well in clinical trials on 2,000 patients throughout the world, and that it has been used to treat 200 patients in the UK with great success. But it will be interesting to see whether in attempting to eliminate the adverse side-effects, Janssen has sacrificed some of the antipsychotic efficiency of the standard drugs. Although the drug is claimed to be effective in only a single daily dose, it is not suitable for treatment of manic schizophrenia.

Research into the causes of schizophrenia is at present in a state of limbo, but the efficiency of Orap as an antipsychotic agent may help to underline the suspicion that dopamine may be involved in schizophrenia. The primozide drugs are specific blockers of dopamine neurones, and the use of the drug will be watched with interest by biochemists looking into the biochemical basis of schizophrenia.

VIRAL HEPATITIS

Antigen raises Hopes

MUCH of the excitement which gripped immunologists three years ago when it became clear that there is a connexion between viral hepatitis and the presence of Australia antigen in the blood is reflected in a recent report from the World Health Organization (*Bull. Wld. Hlth. Org.*, 42, 957; 1970; HMSO, 6s). There is no sign that this excitement is cooling down; next week in *Nature New Biology*, Józwiak and his associates present the first evidence that RNA is associated with the antigen particle, a discovery which goes some way towards proving that Australia antigen is, in fact, viral in nature.

Viral hepatitis—acute inflammation of the liver caused by viral infection—takes two forms, epidemic and serum, by virus A and virus B respectively. In

spite of more than 40 years of research, no specific laboratory or diagnostic test for either form of the disease was developed until 1967 when Blumberg and his associates noted the frequency with which Australia antigen—discovered in the blood serum of an Australian aborigine by Blumberg some years earlier—was present in the blood of sufferers from serum hepatitis.

The value of this discovery was twofold. First, it provided a new way of tackling the apparently insoluble problem of viral hepatitis. Second, it meant that by using a series of laboratory tests it became possible to detect the antigen and its corresponding antiserum in human blood. This is of great importance to blood transfusion and similar services, for the early detection and exclusion of blood donors carrying the antigen might significantly reduce the risk of hepatitis from transfusions. At first, it seemed that screening all potential donors for the Australia antigen would reduce the risk of hepatitis to the recipient by only 25 per cent, but as more sensitive laboratory tests are developed, this percentage must increase. The new report reviews a number of these techniques; at present, it seems that radioimmunoassay is potentially the most sensitive method for the detection of both antigen and antibody. In this test, purified antigen labelled with radioactive iodine is allowed to form a complex with the corresponding antibody. The ratio of complexed to unbound antigen can be estimated by gamma-ray counting, and the antibody can thus be detected by its ability to form complexes with the antigen; similarly, the Australia antigen can be detected by its ability to displace labelled antigen from a standard quantity of antibody antigen complex.

Unfortunately, Australia antigen is specific only to serum hepatitis which represents rather less risk to the population than the epidemic form. A graphic illustration of the virulence of the disease was the outbreak in Edinburgh last year, when eleven patients and staff died in the city's hospitals. Nevertheless, the intense interest which Australia antigen has focused on the problem of viral hepatitis must undoubtedly have far-reaching consequences for future research into this disease.

MATHEMATICS

Teaching Methods

from a Correspondent

A CONFERENCE sponsored by the Institute of Mathematics and its Applications attracted some 180 participants to University College, London, last week. The need for defining aims, and for facing the

inevitable changes that will become necessary in the teaching of mathematics were constantly emphasized throughout the conference and discussion ranged widely over topics which included examinations, computing, television and other aids, and ended with a look at the role of mathematics in higher education during the 1970s.

The scheduled speakers and impromptu participants in the discussion devoted much attention to ways in which the mathematical needs and interests of students could best be catered for. Professor H. Halberstam (Nottingham), in particular, pointed out the advantages of involving students in the actual teaching process, for example by dividing students into smaller groups who, after directed reading, could exhibit different presentations of the material. There was also much emphasis on the need for problems whose clear relevance to "real life" could provide the motivation for development of basic themes *en route*.

A series of talks led by lecturers from polytechnics included a detailed and penetrating study of examinations by Mr J. A. P. Hall (Hatfield) who gave considerable support to the views expressed by the National Union of Students. He concluded with a number of questions: Why not use oral examinations to help to decide in borderline cases? Why not abolish the system of announcing honours results in the three traditional grades?

The final session of the conference was given over to a discussion of modern teaching techniques, in which the Open University inevitably played a leading role. In particular, it was pointed out that the Open University is attempting to present mathematics as a unified subject to an abnormally heterogeneous population of students. But of more relevance to existing universities was the discussion by Dr C. C. Bartlett (Strathclyde) of the use of video tape for giving lecture courses to large numbers of students in science and engineering. They are given essentially a standard lecture but the saving in staff time enables much closer contact to be made with students in comparatively small tutorial groups.

NETHERLANDS

Coordination Needed

A REPORT submitted recently to the Dutch government by the Science Policy Council should dispel any lingering illusions that a final solution to the problems of guiding science can be achieved merely by setting up a body of eminent scientists to advise on national science policy. In the council's own words, the measures that were adopted four years ago, when the SPC was established, were "insufficient to produce a national science policy for different areas of concern". It is therefore no surprise to find the council advocating

the implementation of further measures for coordinating the scientific activities of various government ministries.

But, to some extent, the Science Policy Council's advice is not as far-reaching as it should be. Firmly clenching its fist to deal a sharp blow to the very structure of the government ministries, the council says that it "wonders if the whole decision making process of the government, the inherent government structure and the implementation of the government machinery are not rather questionable". But, with the help of some rather inelegant footwork, the council pulled its punch, and decided to "limit itself to searching for optimization within the possibilities existing in the present constitutional situation, without giving its opinion on whether alterations in this respect are desirable".

This decision effectively accepts that individual ministers will retain responsibility for the scientific research programmes in their own departments, and the problem becomes one of ministerial coordination. But the Science Policy Council considers that this is no bad thing. Believing that government ministers should be responsible for the objectives of their ministries, the SPC sets its face against any suggestion for establishing a separate ministry for science because this would divorce scientific research from well-defined departmental goals.

What, then, is to be done to evolve a coherent science policy? The SPC has few suggestions to offer, except to exhort the government to intensify the informal ministerial deliberations on science policy, and to extend the activities of the Standing Interdepartmental Committee on Science Policy. This committee, the council suggests, should be composed of senior civil servants who are well versed in scientific matters and who are involved in ministerial policymaking.

The Science Policy Council does, however, float one idea for coordinating science policy at the policymaking level. It recommends the creation of a special General-Directorate, whose task should be "the coordination of science policy and the support of extramural university research in general, as far as this is not incorporated in some other ministry's function". The directorate, the SPC suggests, should be linked to the Ministry of Education and Science.

Finally, unable to resist the temptation to discuss the government's decision-making process, the SPC advocates the appointment of three secretaries of state who should be attached to the Ministry for Education and Science: one for primary and secondary education, one for university education, and one for national science policy. The latter should have political responsibility for a "diversified programme of science policy", and direct responsibility for a number of scientific agencies and institutes.

NEW WORLD

Academy Critic Shoots Wildly but Hits Sore Spot

by our Washington Correspondent

EMOTIONS ranging from surprise to anger and indignation have been the response in the National Academy of Sciences towards the institution's latest critic, former Secretary of the Interior Stewart L. Udall. "A bit thick", was the opinion of one academy officer last week of Udall's remarks; "Inaccurate and intemperate", was the verdict of another; and the president of the academy, Philip Handler, calls Udall's attack "ill considered, unfounded, unnecessary, gratuitous, unwise".

The warmth of the academy reaction stems from what is seen as the unfairness of Udall's outspoken comments, which primarily criticize the academy for not having raised its voice earlier and louder in defence of the environment. A second prong of the former secretary's attack is directed at the academy's relationship with government, a more sensitive and complex issue which has been the subject of debate within the Academy.

Udall, who was Secretary of the Interior throughout the Kennedy and Johnson administrations, is now head of an environmental consulting agency in Washington called the Overview Group. Choosing as the platform for his remarks the meeting in Chicago last month of the American Association for the Advancement of Science, he accused the scientific community and the National Academy in particular of "having worn blinkers when viewing the relationship between science and society" and having failed, individual exceptions apart, to alert the public to the dangers of technological advance. Udall chided the academy for having adopted a passive interpretation of its obligation to provide advice to the government, making the technical assessments asked of it but withholding opinion on the wider issues, to the extent that it had become a "puppet" or "mere adjunct" of the institutions it served. As specific examples, Udall said the academy had provided a "convenient rationale" for "the SST lobby, highway contractors (and) the Defense Department". Another specific criticism is the charge that the academy helped recruit young scientists to work on chemical and biological warfare. Udall criticized the president of the academy in person for having tried to put down as scientific upstarts certain scientists who had spoken out on environmental issues. Finally, he proposed that the public interest lawyer Ralph Nader should make an intensive study of the

National Academy and "the whole scientific enterprise".

Asked last week how he would propose to reform the academy Udall said he did not have any specific ideas—"I made the speech because the scientists I have talked with share the opinions I expressed. I have not made a detailed study—I may have overstated the case, I don't know." Udall explained that what was needed in his opinion was "a scientific organization not only concerned about the future and the environment, but also able to act as a counterforce to government, expressing its own judgements and telling the nation how to use science to solve its problems." Individual scientists are afraid to speak out, Udall believes, because of repression from above—"The academy through its ties with the National Science Foundation controls all the research grants, so nobody will speak up. Also, scientists want to get into the academy but a man who criticises won't get in—the system is a very cosy one." The former Secretary quotes with approval the remark of a council member of the academy who told him that "the academy is limited, but it should continue to do what it is doing and we should have another organization which is more independent, more of a gadfly".

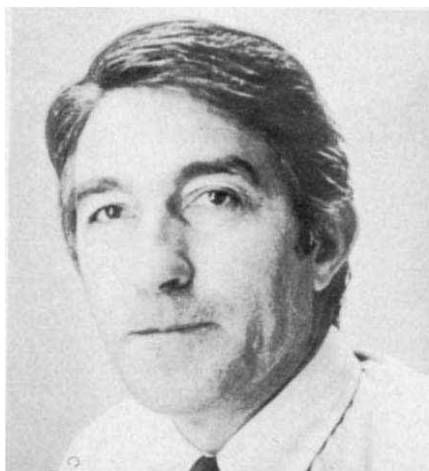
To some of these criticisms the academy gives short shrift; to others, the answers are rather longer. On the issue of chemical and biological warfare, for example, the academy denies having recruited staff for the army's laboratories; what has been done is that the academy, through its office of scientific personnel, manages a series of fellowship programmes at government laboratories, among which was a "modest postdoctoral programme" for Fort Detrick, the army's chief biological warfare laboratory, now to be closed down. Detrick was included on the Academy's programme because of its special scientific facilities. Among the conditions of the fellowship programme was the stipulation that in no case were the students to work on classified material or research with military applications. "When this programme was set up," Handler said last week, "the attitudes in the nation were such that it seemed like a completely reasonable thing to do."

Commenting on the academy's position with respect to the supersonic transport, Handler says that it was an academy report (*Human Response to*

Sonic Boom, issued in 1968) that first stated clearly that the sonic boom would probably rule out overland flights. Under the National Academy of Sciences, the highway research board carries out research for the highway commissions of the fifty states—"but that doesn't make us lobbyists for or against the highway contractors", Handler says. As for military research, Handler is adamant that the academy must give advice to the Department of Defense as long as the need for a Department of Defense exists.

It is Udall's comments on the environmental issue that have aroused the deepest indignation, particularly since the blame for any neglect of the environment in recent years, in the academy view, lies rather with Udall than the academy. The then Secretary of the Interior "didn't lift a finger" to implement any of the recommendations made by an NAS committee in 1962 which, Handler claims, says everything there is to be said about the threat to the environment. "In April 1966," Handler continues, "we produced a remarkable report on waste management and control. If Udall had had the wit to implement that report he would be a national hero. It was Udall who signed the oil leases off Santa Barbara, the results of which we are still paying for, and he also signed the leases for drilling in the Gulf of Mexico. Udall never asked our opinion on whether this was a wise thing to do." Handler adds that during Udall's secretaryship most of the work done by the academy on the environment was undertaken at its own initiative—"Udall seems to have discovered the environment after he left his post as Secretary of the Interior."

Although Udall may have done less than full justice to the academy's efforts on behalf of the environment, he is not alone in questioning the nature of the academy's relationship with government and with the Department of Defense in particular. This is an issue which has been raised by members of the academy as well, some of whom are also critical of what they describe as the academy's "recognisably undemocratic" constitution and modes of operation. The charter of the academy, approved by Abraham Lincoln, obliges it to report on any subjects of science or art whenever called upon by any department of government. Thus as well as being an elitist body of the nation's most eminent scientists the Academy has the additional responsibility, unusual for a



Stewart L. Udall

learned society, of tendering advice to government including in particular military advice. Handler indeed notes that "if we ever won our spurs, it was during World War II".

Although the academy is insistent upon its independence, it is often assumed by the ignorant to be a branch of government, since the government is its only customer and accounts for the bulk of its activities. Lack of any appreciable independent income is one reason why the academy only seldom speaks except when it is spoken to, a posture which is regretted inside the academy as well as without—"I would accept the thesis that the academy has been insufficiently purposeful in generating its own agenda for action", Handler says. It is only recently, however, that the academy's necessarily intimate ties with its only client have been looked at askance. One of the chief issues raised by Udall and others before him, the terms on which a government request for advice is accepted, has also been of concern within the academy. One staff member says it is certainly true that from time to time academy committees have taken on too narrow a brief. George Kistiakowsky, vice-president of the National Academy and former science advisor to President Eisenhower, cites as an example a contract accepted under the academy's previous president which asked the academy to advise on the physical quality of the sonic boom without commenting on its possible dangers. "This put the academy in the position of seeming to endorse the SST," he says. But it is unfair to condemn the academy for this sort of past error, Kistiakowsky believes, since "under Handler there has been a very systematic and careful effort to ensure we don't accept contracts on terms of reference which put us in an unfortunate position." And in rebuttal of Udall's portrayal of the academy as a "puppet of government" Kistiakowsky said last week "I assure you I am *not* a

puppet of the Nixon Administration—please underline the *not*".

A safeguard on academy reports is the Report Review Committee, which was set up by Handler in March last year and has been in operation since July. Chaired by Kistiakowsky, the committee gives an independent assessment to all reports produced by academy committees before they are released. One of the committee's chief objectives is to see that academy reports are complete and do not neglect relevant issues.

A more specific issue which has been of particular concern to certain members of the academy is the propriety of accepting classified work. For instance George Wald, professor of biology at Harvard University (and a member of the academy since 1950) says of the academy's involvement in classified matters, "All of us feel that this would be wholly proper if it were the defence of the nation that were at stake. The present problem is whether we should regard certain of these activities as defence. If they are aggressive, one wonders what business the academy has to be involved in them". Citing the academy's commitment not just to national ends but to "humanity at large and to science", Wald believes that specific guidelines should be laid down to define the academy's relationship with government. "The obligation in the charter to advise the government is constantly being emphasized, as though we were a limb of government". Wald says: "This is far too narrow, considering what the academy should represent and does represent".

A more radical member-critic of the academy is Richard C. Lewontin, professor of biology at the University of Chicago, who says he agrees with the sense of Udall's remarks and has been "fighting the same battle". The officers of the academy, he believes, "want to be deeply involved in the administration of science and they are very loath to take any steps that would jeopardise their influence with the President's Science Advisory Committee such as disengaging their services to the military". At the annual meeting of the academy in April last year Lewontin introduced a resolution to the effect that the academy should refuse to take on any more classified work. Although there were only a handful of votes in favour, Lewontin says he will introduce the resolution again this year.

Critics of the academy's role in military affairs quote as an admittedly extreme example of its attitude the situation that if asked by the government what kind of gas to use in gas chambers the academy would do a study and determine the most efficient gas. "If you believe that you also have to believe we are living in Nazi Germany",

says a staff member, who adds that in his opinion probably every academy member would refuse to participate in any study of napalm, for instance. As it happens both the two chief officers of the academy have taken steps to limit their personal involvement with military affairs. Kistiakowsky, the vice president, resigned in March 1968 from all Department of Defense committees because in his opinion the department had become so separated from the national interest. And Handler on becoming president of the academy refused to occupy the seat held by his predecessor on the Defense Science Board, which advises the Director of Defense Research and Engineering.

One point on which both Wald and Lewontin disagree with Udall is in his charge that the academy represses dissent within the scientific community by acting to withhold research grants or refusing to elect iconoclasts into its ranks. "This sounds weak to me", Wald says; "it simply doesn't ring true". In Lewontin's opinion the academy through those of its members on the National Science Board (the governing body of the National Science Foundation) may influence priorities between major fields but the awarding of individual research grants is done by peer review panels who "do not cut individual throats". As for election into the academy, Lewontin says there may exist a "self-perpetuating conservatism, but this is a reflection of the collectivity rather than any conspiracy".

HARVARD

Mediator Elected Head

DEREK C. BOK, the forty year old dean of the Harvard Law School, was elected president of Harvard University this week to succeed Nathan M. Pusey. Bok, a specialist in labour and anti-trust law, is well liked among faculty and students at Harvard, and is one of the few university officers to have survived relatively unbloodied through the upheavals of the past two years.

The search for a new president began in February last year when Nathan Pusey, president for eighteen years, announced he would resign. An intensive search was put on foot by the thirty-man board of overseers who produced a list of 900 names, which by last month had been whittled down to twenty-three, with Bok already as favourite.

Bok comes to the presidency with a reformist reputation gained during his two years as dean of law school, where he expanded the curriculum and dealt successfully with student demands for changes in the examination system. An immediate problem facing the new president will be the financial troubles with which Harvard, like most other universities, is beset.

NEWS AND VIEWS

Changing Dinosaurs—but not in Mid-stream

THE dinosaurs are still evolving—or, at least, our view of their way of life is still changing. Twenty to thirty tons in weight and nearly one hundred feet long, the great herbivorous dinosaurs known as sauropods are inevitably the most impressive exhibit in any natural history museum that is large enough to house them. Almost any book about dinosaurs will have a reconstruction of such a sauropod as *Apatosaurus* (often incorrectly called *Brontosaurus*), half submerged in a lake and inaccessible to its great carnivorous relatives such as *Tyrannosaurus*, while placidly browsing on soft aquatic plants.

Some questioning voices against the belief that the sauropods were aquatic have been raised in the past. Dr Kenneth Kermack of University College, London, pointed out twenty years ago that if one of these animals had stood on the bottom of a deep lake, as is so frequently shown in illustrations, with its neck stretched upwards so that its head reached the surface, then its thorax would have been at a depth of about twenty feet.

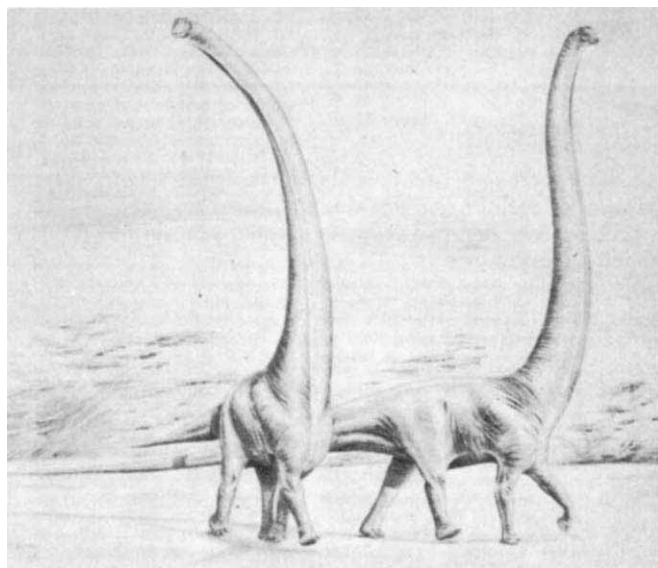


Fig. 1 Bakker's restoration of the sauropod *Barosaurus* which was about 85 feet long and about 40 feet high (from *Discovery*, Peabody Mus., 3, 15; 1968).

On page 170 of this issue of *Nature*, Robert Bakker of Yale University convincingly demolishes the belief in the aquatic mode of life of sauropods. He discusses the size of their nostrils, the wear of their teeth, the shape of their body, the structure of their vertebral column, limbs and feet, and the sedimentology of the beds in which they are most common. He concludes that none of these features support the accepted view of their habits, and that they instead unequivocally indicate that the sauropods lived on land and fed on fairly coarse food.

If sauropods were land dwellers, why did they have long necks? Bakker points out that both the largest extinct mammals and the largest living ones are adapted for browsing over a greater vertical range of food than is accessible to shorter herbivores. A long neck is of little use to an aquatic herbivore, because water plants do not grow at great depths—the living hippos are notably short

necked. It seems, then, that the sauropods were reptilian giraffes, browsing off the conifers and cycads which have been found in the same deposits.

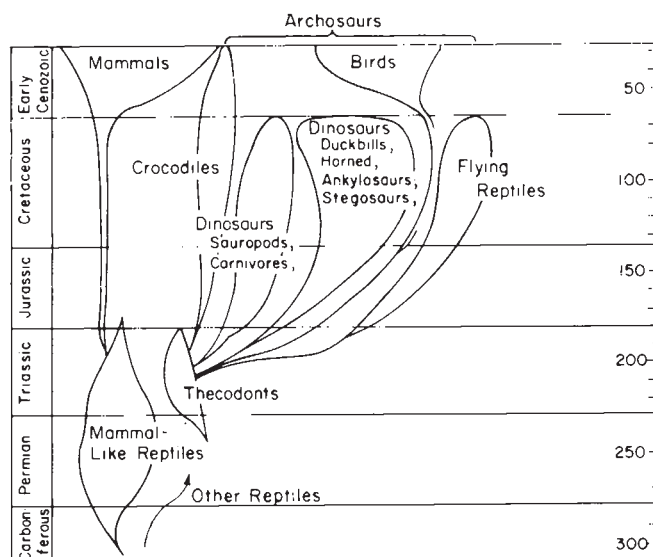


Fig. 2 Relationships of dinosaurs to mammal-like reptiles and the early mammals. Numbers at right indicate millions of years before present (from *Discovery*, Peabody Mus., 3, 12; 1968).

If it was not their inaccessibility in the water that made the sauropods safe from the attentions of carnivores, how did they protect themselves? Bakker, in an earlier article (*Discovery*, Peabody Mus., 3, 11; 1968), suggested that they could swing the long, muscular tail with a force sufficient to severely injure an attacker, and also rear on their hind limbs and use their fore limbs to strike at or to crash down upon their adversary. A herd of such creatures must have been formidable though, as Bakker shows in his restoration (see Fig. 1), they probably had to hold their tails clear of the ground to prevent other members of the herd stepping on them!

It is interesting to note that the sauropods are not the only dinosaurs which palaeontologists have recently dragged ashore. The sauropods belong to the Saurischia, one of the two great independent groups which together make up the assemblage popularly called dinosaurs. The other group, the Ornithischia, also includes a family, the duckbills or hadrosaurs, which were thought to be aquatic or, at least, amphibious. Dr. John Ostrom, also of Yale University, showed in 1964 (*Amer. J. Sci.*, 262, 975) that, like Bakker's sauropods, the hadrosaurs were largely terrestrial and probably browsed on land plants.

If the sauropods were really terrestrial, the anti-continental drift lobby has thus lost another small prop. Until now, the presence of sauropods in areas now violated by sea, such as Madagascar and Australia, required little explanation: such semi-aquatic animals could surely have swum there, as may the living hippo of Madagascar. Now that the sauropods seem to have had as little long distance swimming ability as the elephant, we can conclude that they instead reached these areas by the dry-land routes which the geophysicists have now thoughtfully provided.

FRESHWATER FISH

Pollution by Introduction

from our Marine Vertebrate Correspondent

IN spite of all the recent concern over our polluted environment, there are glaring gaps in our defences. Something is now known about the pollution of the native biota in North America by the introduction of exotic animals and plants. E. A. Lachner, C. R. Robins and W. R. Courtenay jun. (*Smithson. Contrib. Zool.*, **59**, 1; 1970) show that twenty-five non-indigenous species of fish have been introduced and established in the United States and Canada. Some are imports of long standing; for example, the European brown trout arrived in the 1880s and the carp half a century before. Both these fish were officially sponsored introductions of food or sporting value, but the carp, in particular, has proved to be one of the most disastrous aquatic introductions made, and considerable sums have been spent in recent decades by some States to control the fish in their waters.

So-called fisheries management by introductions, transplantations and hatchery interbreeding of trout stocks has effectively destroyed many of the native trout populations of the west coast of the United States. At least thirty-three nominal species of trout had been described (often inadequately) and the ecology and biology of many remain unknown. Among those now extinct are the emerald trout of Pyramid Lake, Nevada (*Salmo smaragdus*), and the royal silver trout (*S. regalis*) of Lake Tahoe, California and Nevada.

Lachner *et al.* report the greatest biotic pollution in North America to be in the State of Florida, which they describe as a biological cesspool of introduced life. As many as fifty-seven species of exotic vertebrates are numbered in the fauna of Florida, ten of which are well established fish species. Several species of cichlid, from both South American and African stocks, are now widespread in the state, and are thriving, it is feared, at the expense of native fish. Some of these cichlids have been released with the object of improving sport fishing; others are the result of accidental escapes from the stock ponds of aquarium fish dealers. One of the most potentially damaging of the second category is the release of the Asiatic walking catfish, *Clarias batrachus*, a fish which reproduces prolifically, has rapid growth, maintains itself in dense populations, and can distribute itself easily through waterways or overland. A member of the Florida Game and Fresh Water Fish Commission is reported to have said that this fish is out of control, and that there is no practical method of eradication available.

Lachner *et al.* also comment on the Asiatic grass carp, *Ctenopharyngodon idella*, a gross browser on aquatic

vegetation, the feeding habits of which have great international appeal as a "cheap" method of keeping open waterways. This fish has been imported into the United States and is being kept in ponds by many federal, state and other agencies. Its establishment in the open waters at least in the south would seem to be a serious possibility, and as Lachner *et al.* conclude, it could become a serious pest, perhaps more so than its near relative the carp has proved to be. It is as well to remember that the carp was introduced and protected in the eighteenth century by the then federal authorities, so the same sponsors for the grass carp are no guarantee that it could not prove to be another expensive introduction.

ORNITHOLOGY

Wild Mynah Calls

from our Animal Behaviour Correspondent

THE remarkable imitative powers of the Indian hill mynah (*Gracula religiosa*), which make this bird such a popular pet, are the subject of a recent investigation by Brian Bertram (*Anim. Behav. Monogr.*, **3** (2), 81; 1970). His study, carried out

in Assam in north-eastern India, reveals some curious facts about the vocalizations of wild mynahs. For instance, although adult mynahs are seen in pairs for much of the year and pairs of birds breed together in successive years, a bird does not imitate its mate. Each mynah has between five and twelve "calls", but each member of a pair has a completely different call repertoire. Birds will, however, tend to make at least some of the same calls as those made by neighbouring mynahs of the same sex. There are thus distinct local dialects confined to one sex. Young mynahs imitate the calls of adults but, surprisingly, probably do not imitate other species, for no wild adult was ever heard to imitate any species but its own. This means that mynahs presumably have some means of recognizing the sounds of their own species in spite of the great variation from one individual to another. The fact that captive mynahs so readily imitate human noises is, Bertram believes, because human whistles and our low-pitched voices are very similar to wild mynah calls.

Variation between the calls of one individual mynah and another, combined

Arguments about Ageing

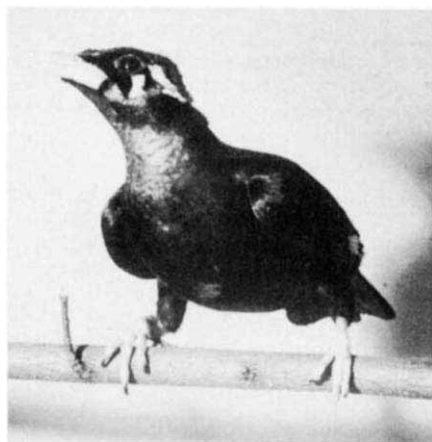
BROADLY speaking, there are two major theories about the mechanisms of ageing; one proposes that the process is genetically controlled and allied to development, and the other suggests that the major factor involved is random cell damage mediated either by mutation or through errors in protein biosynthesis. There is no conclusive evidence in support of either hypothesis and two recent reports do not really throw much light on the matter.

The evidence provided by Lints and Lints in next Wednesday's *Nature New Biology* suggests that the first idea might be the most tenable, because interference with development during the larval stage of *Drosophila* subsequently affects the lifespan of the adult. In one of their experiments batches of larvae were maintained at different temperatures and, as might be expected, because the body temperature of the larva is controlled by that of its environment, it was found that development was delayed in those batches kept at the low temperatures. The interesting point, however, is the effect which this subsequently had on lifespan, for lengthening the developmental period increased the life of the adult. They have also shown that the developmental period can be prolonged when the larval population density is high, and again this is reflected in increased longevity. Their work thus suggests that the first of the theories might be correct, but it has also been shown recently (C. M. Lewis and R. Holliday, *Nature*, **228**, 877; 1970)

that cellular damage resulting from errors in protein biosynthesis can cause death.

Lewis and Holliday have shown that in two senescent mutants of the fungus *Neurospora*, death is preceded by an accumulation of altered protein, presumably resulting from errors in protein biosynthesis. The presence of amino-acid substitutions was demonstrated by an increase in the thermolability of glutamic dehydrogenase enzyme and the extent of the altered protein was determined by measuring the relative amount of immunological cross reacting material. The most interesting of their findings, however, was the association of a high mutation rate with the increasing alteration in protein and they suggested that this was mediated by changes in enzymes concerned with DNA synthesis. Death in this instance might therefore result from errors in either protein or the hereditary material.

This work with *Neurospora*, although it provides evidence that alterations in cellular proteins can accumulate and cause death, does not necessarily have a direct bearing on the mechanism of ageing in higher organisms. Neither, however, as the Lints point out, does the fact that increasing the lifespan by "stretching" the developmental programme necessarily mean that ageing is genetically controlled. It is possible that the two theories are not mutually exclusive, for a factor which has not yet been ruled out is whether the frequency of errors is under genetic control.



Indian hill mynah. (Photo: Zoological Society of London.)

with the capacity to imitate neighbours, indicate that these birds could potentially recognize a large number of different individuals and even recognize the locality of a bird which is not known individually. But why this should have evolved in mynahs so much further than in most other species of birds is still not known.

ENZYMES

And Now Hysteresis

from our Molecular Biology Correspondent

THE dwindling band of biochemists who have kept pace over the years with the ramifications of cooperativity, allosterism and induced-fit in complex enzymes, will not, one imagines, be best pleased by the suggestion that these all represent a gross and obvious oversimplification of the real situation. Such, however, is the message of an important new paper by Frieden (*J. Biol. Chem.*, **245**, 5788; 1970), which ends with the hope that the new concepts that it introduces will in the end be seen to simplify, rather than complicate, the interpretation of metabolic regulation—a desire which will surely be weighed in its author's favour on the day of judgment.

Frieden makes the point that essentially all theories that treat of control of enzymic activity by non-competitive ligands, and the anomalous dependence of initial velocity on the concentration of such ligands or of substrate, make an unstated assumption. If the enzyme exists in conformational equilibrium between states of different enzymic characteristics, the possibility exists, and has so far been disregarded, that the rate of interconversion between the states may be slow relative to the formation of products. It is in fact already established that structural adjustments are indeed slow in many systems, most obviously perhaps in cases where they take the form of association or dissociation of the protein subunits. Frieden views such instances of slow equilibration as hysteresis effects, in which the measured

catalytic rate after introduction of a modifying ligand, for example, is compounded of contributions from the state which is stable only in the absence of that ligand, and the state to which the ligand causes a slow transition. He formulates in these terms a number of models of varying complexity, in particular for systems involving the synthesis of a feedback inhibitor to which the enzyme responds in hysteretic fashion. Instead then of abruptly switching off, the enzyme buffers the effect of the change in inhibitor concentration. If the response were fast, the supply of metabolites produced by such an enzyme in a complex pathway would be instantaneously cut off, with perhaps dire results. There is no shortage of likely examples of hysteresis in action. One on which Frieden expatiates is the aspartate utilization scheme, worked out by Stadtman for *E. coli*, in which the feedback inhibition of homoserine dehydrogenase activity by threonine blocks also the production of methionine, and therefore normal growth. If the response to threonine were slow, on the other hand, the methionine concentration would remain sufficient for long enough to prevent the machinery from stalling while the threonine level once more regulates itself. Similarly the concentration of isoleucine is controlled at a

remove by that of threonine, and the former is a feedback inhibitor of another activity, that of threonine deaminase. If the latter process is also slow, a rapid accretion of isoleucine will not bring about a catastrophic drop in the concentration of the other products dependent on the pathway, threonine, methionine and lysine.

Frieden finally makes the point that a change which is fast in relation to one pathway may be small on the time scale of another. Thus a slow change in the concentration of a metabolite may still be rapid compared with the hysteretic adjustment of the activity of an enzyme that it controls. One is persuaded by the numerous available examples of slow events in enzymatic systems that the hysteresis concept is likely to be of general importance, at any rate in complex, interlocking metabolic pathways, and it will no doubt be widely used to explain the inexplicable.

A good example in the current literature of conformational steps that are slow in relation to the rest of the catalytic scheme is to be found in the work of Shore and Gutfreund on liver alcohol dehydrogenase (*Biochemistry*, **9**, 4655; 1970). Here the dissociation of NADH may be followed under appropriate conditions by the stopped-flow method,

Repair and DNA Polymerase

The idea that the DNA polymerase of *Escherichia coli*, discovered by Kornberg and until recently thought to replicate DNA, is instead an enzyme concerned with the repair of damage in DNA, is lent further support by two articles in next Wednesday's *Nature New Biology*. It has previously been shown that the Cairns mutant of *E. coli*, which is defective in DNA polymerase activity when assayed *in vitro*, is unusually sensitive to the damage in DNA caused by irradiation with ultraviolet light, and Witkin and Klein and Niebch have used this mutant to try to pin down exactly which step in repair is affected by the lack of DNA polymerase.

When cells are irradiated with ultraviolet light, adjacent thymine bases in DNA are covalently linked together to form "thymine dimers". These dimers distort the structure of the DNA double helix, and many types of cell have now been shown to possess "excision-repair" systems which remove the dimers from DNA and replace them. But although DNA polymerase can excise the dimers from ultraviolet irradiated DNA *in vitro*, the excision of dimers has previously been shown to be normal in the mutant.

This suggests, of course, that DNA polymerase may be part of some other repair system. Witkin has studied the induction of mutations by ultraviolet light in the Cairns mutant; these muta-

tions are caused by the attempts of another repair system, which is very error-prone, to fill the gaps which are left when DNA containing unexcised thymine dimers is replicated. But the number of mutations is the same in the mutant and in normal *E. coli*, so DNA polymerase cannot be part of the repair system which is error prone.

Bacteriophages which have been damaged by ultraviolet irradiation can be repaired by the host excision-repair system during infection of bacterial cells. Klein and Niebch show that phages ϕ X174 and λ are repaired less efficiently by the Cairns mutant than by normal bacteria. This means that DNA polymerase must be part of the excision-repair mechanism which acts on bacteriophages. When the host cells have been mutated in one of the genes coding for the enzymes of this system, addition of a mutation in the DNA polymerase gene does not make repair any less efficient. This confirms that DNA polymerase belongs to the same system as the enzyme coded by the other mutated gene.

The only firm conclusion to emerge from these data is that DNA polymerase is concerned with excision-repair, but acts at some stage after the thymine dimers have been excised. Just what it does, and why this is important for proper repair of damaged bacterial or bacteriophage DNA, remains to be established.

taking advantage of the change in fluorescence on binding. It turns out to be too rapid to account for the catalytic rate, and a rate-determining isomerization of the enzyme-NADH complex is indicated. The rate of appearance of the bound NADH is fast by comparison, and results with deuterated substrate show that the rate reflects that of the hydride transfer step from ethanol itself. The presence of two different rate processes is also obvious from temperature-jump relaxation experiments.

DNA PRECURSORS

Down to the Pool

from our Cell Biology Correspondent

IN many a laboratory where animal cells are cultured, questions about the sizes of the intracellular pools of such precursor molecules such as nucleotides and amino acids bring shifty glances, nervous smiles and a rapid change of subject. The fact of the matter is that countless investigations of the synthesis of proteins and nucleic acids in animal cells, either uninfected or infected with viruses, have been and are being made in almost complete ignorance of the sizes and characteristics of relevant precursor pools. For most cells we do not know how rapidly a radioactive precursor added to the medium equilibrates with the intracellular pool; we do not know the size of the pool; we do not know if different species of macromolecules are synthesized from the same precursor pools; and finally, we have little information about the kinetics of breakdown of macromolecules and re-utilization of their subunits.

Thanks to Lindberg and Skoog (*Anal. Biochem.*, **34**, 152; 1970) we now have, however, a sensitive enzymatic assay for deoxynucleoside triphosphates which Nordenskjöld *et al.* (*J. Biol. Chem.*, **245**, 5360; 1970) have exploited to measure the pools of dTTP and dATP in secondary cultures of mouse embryo cells; their experiments are an object lesson to those who aspire to carry out experiments with eukaryotic cells which are as rigorous as those which have been done with *Escherichia coli* and its phages. If the lead which Nordenskjöld and his colleagues have given is pursued, it may not be long before cell biologists can talk of amounts of nucleic acid or protein made rather than the number of counts per minute incorporated.

According to Nordenskjöld *et al.* the average size of the pools of dTTP and dATP in mouse embryo cells in culture at the peak of DNA synthesis is 3.0 and 2.5 pmoles per μg of DNA. This, they say, means that the intracellular pools of these two DNA precursors are, at their maximum, sufficient to permit 2 to 4 min of DNA synthesis, which should console those who have tried to label in pulse

chase experiments the DNA made, for example, in mouse embryo cells infected with polyoma virus.

Nordenskjöld and his colleagues have also measured the changes in size of these two pools as DNA synthesis is induced in a culture of resting cells. In short they find that after a period of serum starvation, during which DNA synthesis in most cells declines to a low resting level, the pools of both precursors drop to about 0.5 pmoles. When DNA synthesis is then triggered by either polyoma virus infection or the addition of serum to the cultures, the size of the precursor pools increases in parallel with the rate of DNA synthesis; interestingly the pools of dTTP and dATP never increase before the onset of DNA synthesis, indeed the pool of dTTP actually falls as DNA synthesis begins. Likewise the activities of two enzymes involved in nucleotide metabolism, thymidine kinase and ribonucleoside reductase, increase in parallel with increasing DNA synthesis. In other words initiation of DNA synthesis does not seem to result from an increase in the pools of nucleotides; rather it seems that such increases are a secondary result of an increase in DNA synthesis.

Further analyses such as these to include the other two DNA precursors, dCTP and dGTP, and other types of cells are highly desirable, and with improved techniques for synchronizing cell populations it should be possible to

obtain even more rigorous data. Further, if comparable assays can be developed for ribonucleotides, many of the outstanding questions concerning the synthesis of RNAs, particularly in cells infected with transforming viruses such as polyoma virus, might be answered.

Not content with developing or awaiting the development of techniques for cell synchronization, Robbins and his colleagues have been investigating ways of mimicking at least the early stages of mitosis by subjecting HeLa cells to hypertonic conditions. Last year (see *Nature*, **226**, 14; 1970) I drew attention to their report which showed that such treatment irreversibly induces in HeLa cells many of the morphological changes which characterize mitotic prophase. Now Pederson and Robbins (*J. Cell. Biol.*, **47**, 734; 1970) claim that the parallels between HeLa cells in mitosis and in hypertonic media extend beyond mere morphology. Comparisons of the pattern of RNA synthesis in a synchronized culture of HeLa cells going into authentic mitosis and randomly growing culture placed in hypertonic media indicate that in both cases the synthesis of heterogeneous nuclear RNA is preferentially inhibited and that the processing of 45S ribosomal precursor RNA is slowed. Synthesis of transfer RNA on the other hand is resistant to inhibition by hypertonicity and it also continues to some extent throughout mitosis. It seems that the simple expedient of changing the

Micropulsations and the Plasmopause

IN next Monday's issue of *Nature Physical Science*, H. Kikuchi suggests that the measurements made by the OGO 3 satellite of fluctuations in the plasma density, at altitudes greater than 20,000 km above the Earth's surface, are linked with rather regular oscillations in the Earth's magnetic field observed on the ground.

The OGO 3 measurements have shown that the ion concentration does not vary smoothly with distance from the centre of the Earth; often the proton density changes by more than an order of magnitude in quite a short distance. This discontinuity is called the plasmopause and in the equatorial plane the "knee" in the plasma distribution occurs at about 4 Earth radii on days of moderate magnetic activity. Apart from the detection of the plasmopause, OGO 3 and OGO 5 (K. K. Harris, G. W. Sharp and C. R. Chappell, *J. Geophys. Res.*, **75**, 219; 1970) have monitored other significant but somewhat smaller fluctuations in the proton density near the plasmopause. Kikuchi now proposes that these fine irregularities may be important in two ways.

First, the plasma density fluctuations might lead to an electrostatic instability which is a possible source mechanism for

Pc 1 events. These pulsations are regular sinusoidal oscillations with periods in the range 0.2 to 5 s (see, for example, J. A. Jacobs, *Geomagnetic Micropulsations*, Springer Verlag, 1970). Occasionally these events persist for hours and exhibit rising "tones" when displayed on a sonagram (graph of frequency against time). Second, the wavelike fine structure in the plasma fluctuations has a periodicity of about 1,000 km, which is comparable with the Pc 1 wavelength in the medium. Thus a duct that will provide some guidance for Pc 1 hydromagnetic waves can be formed between the trough of a plasmasphere fluctuation and the plasmopause.

To summarize, Kikuchi gives some examples of the movement of the plasmopause boundary before and after a geomagnetic storm, and draws attention to irregularities in plasma distribution within the plasmasphere which existed at about the time that Pc 1 pulsations were observed on magnetic records at a ground station. He speculates on the role of the irregularities both as a possible source mechanism for short-period micropulsations and as a hydromagnetic waveguide.

concentration of electrolytes in HeLa cells provides a useful model for analysing the early events of mitosis and that changes in the biochemistry as well as morphology of such cells apparently hinge on the extent to which their chromatin is condensed. Perhaps Robbins and his colleagues will eventually achieve the ultimate goal—the induction of complete mitosis by manipulation of tonicity.

SEISMOLOGY

Earthquake Swarms?

from our Geomagnetism Correspondent

SOME years ago, Mogi (*Bull. Earthq. Res. Inst.*, 41, 615; 1963) found it convenient to distinguish between three types of earthquake sequence. The first comprised a clearly defined large shock accompanied by aftershocks; and the second was similar but with the addition of foreshocks. Mogi's third type was rather different, however, in that there was no large shock at all but only a closely spaced series of events of about the same size. This is the so-called earthquake swarm, a phenomenon which has received comparatively little attention.

The few studies carried out so far have been confined chiefly to continental swarms. And what has emerged from many of them is a clear association with volcanic eruption. Most of the swarms in Hawaii, for example, occur on the summit of Kilauea, an active volcano, and are associated with caldera collapse. So, too, was the large swarm which struck the Galapagos in June 1968. Swarms have also been identified with most of the major eruptions in the Lower Antilles and with volcanic activity in the central Pacific. Usually, however, swarm earthquakes are small. The Richter magnitude of an individual event within a swarm seldom exceeds 6.

But volcanism occurs beneath the oceans as well as on land. Are there therefore any earthquake swarms associated with submarine volcanism? Curiously, swarms originating from the mid-Atlantic ridge have been observed for more than ten years; but until now nobody has chosen to study them in detail or to understand their tectonic significance. Which is surprising, for earthquake swarms are, in fact, characteristic of the world rift system as a whole and are not the monopoly of the Atlantic ridge.

The correlation between oceanic ridges and earthquake activity is, of course, no longer a surprise in itself. But the earthquakes usually thought of in this connexion are individual events (Mogi's first and second types), mostly occurring along fracture zones (transform faults) and characterized by strike-slip faulting. From an analysis of more than twenty

swarms from the mid-Atlantic ridge and the East Pacific Rise, however, Sykes (*J. Geophys. Res.*, 75, 6598; 1970) has discovered that these swarms are restricted to the ridge crests and almost certainly possess large components of normal faulting. Occasionally they occur at intersections with fracture zones but never on the zones themselves. In other words, large earthquakes and earthquake swarms are associated with quite different tectonic features and thus presumably require quite different tectonic explanations.

Not surprisingly, because continental earthquake swarms are often associated with volcanism, Sykes is tempted to suggest that a similar association also applies to ridge swarms as well. Crustal zones of mid-oceanic ridges are, of course, known to be centres of sea floor spreading and

the sources of submarine volcanism. But if the association is valid, does this mean that the mechanism for the production of earthquake swarms is physically related to volcanism? Sykes freely admits that such a relationship is appealing; but points out that it cannot yet be proved. One of the characteristics of the earthquake swarm is its high *b* value—the high percentage of smaller earthquakes—a feature produced by a concentrated stress source which could be, but is not necessarily, the result of volcanism. On the other hand, even the other obvious stress sources are closely related to volcanism. For example, heterogeneous materials and structures are likely to be situated in volcanic regions, and magmas and hydrothermal processes producing high fluid pressures are likely near volcanoes.

The case for the volcanic origin of

Cu(II)-Benzene Complex in Montmorillonite

MONTMORILLONITE, a silicate mineral with typical expanding layers, consists of mica-like sheets that are normally separated by one or two layers of water molecules. The water layers incorporate the exchangeable cations necessary to compensate the negative charge on the planar silicate anions; and polar organic molecules, such as acetone, pyridine, nitrobenzene, and many others, readily replace the interlayer water to give a variety of organic complexes. The organic molecules are either directly coordinated to the exchangeable cation, or held in outer spheres of coordination around hydrated cations by hydrogen bonds (V. C. Farmer, *Clay Miner.*, 7, 373; 1968). Until now, interlayer adsorption of nonpolar organic molecules has been reported only where the exchangeable cation is itself organic.

Mortland and Pinnavaia show in next Monday's *Nature Physical Science* that benzene and other aromatic hydrocarbons will coordinate to exchangeable Cu(II) in montmorillonite under dry conditions. In one form of the complex the benzene structure is more profoundly modified than in any other benzene complex; no other complex between Cu(II) and benzene is known, although Cu(I) does form one. Participation of cuprous ion in the montmorillonite complex is excluded by electron spin resonance measurements.

Infrared spectroscopy shows that two forms of coordinated benzene can be present. In one, benzene vibrations are displaced only 10–20 cm⁻¹ from those of the free molecule. Although these displacements are less than those generally found for typical sandwich complexes, such as Cr(C₆H₆)₂, the interaction between Cu(II) and benzene is thought to be of this type. When this form alone is present, the complex is green. A dark

red complex is formed by more rigorous dehydration, and is characterized by strong, broad absorption bands which are difficult to correlate with those of the free molecule. In addition to bands in the 1,550–1,800 cm⁻¹ region, ascribed to C=C, C–C and C–H vibrations, an intense absorption extends from 1,700 cm⁻¹ to beyond 4,000 cm⁻¹, and is explained in terms of an electronic transition.

The change in infrared spectrum is so great that a new molecular species is suggested. An oxidative degradation would not be unexpected because adsorbed molecules readily oxidize on montmorillonite, and these reactions are promoted by transition metal cations (D. H. Solomon, B. C. Loft and J. D. Swift, *Clay Miner.*, 7, 399; 1968). But this possibility is excluded for the Cu(II)-benzene complex, because the red and green complexes are interconvertible by rehydration and dehydration, and only benzene is liberated when the complex is decomposed with acetone. A structure is proposed for the red complex in which Cu(II) is bonded to an edge of the ring, thus disrupting the aromatic resonance.

The role of the silicate layers in promoting the formation of the complexes is uncertain. Similar complexes are formed in hectorite in which the anion charge is widely distributed over the surface oxygens of the silicate layer, as in montmorillonite, so that the charge on any one oxygen is low. No complex is formed in expanding layer silicates in which the surface charge is concentrated on surface oxygens associated with Al³⁺ substituting for Si⁴⁺ in the silicate layers. It may be that the layer silicate minerals will yet prove as productive a hunting ground for chemists as have the zeolites.

earthquake swarms is thus strong. But there is one crucial difficulty. There are a few swarms which are apparently not related to volcanism at all—the swarm which occurred in the Santa Barbara channel of California in 1968, for example. It is possible, of course, that in such regions there is magmatic activity which fails to reach the ocean floor and which thus fails to be identified as volcanism. On the other hand, there may be ways of producing stress inhomogeneities completely unrelated to volcanism or magmatic activity of any sort. At present, this matter cannot be resolved. In the meantime, Sykes makes a strong plea for on-site investigations of ridge crests soon after swarms occur to see if associated volcanism can be detected.

SPECTROSCOPY

Excited States

from our Molecular Physics Correspondent

THANKS to recent developments in lasers and pulse circuitry, the spectroscopy of transient species with lifetimes in the so-called nanosecond region (10^{-9} to 10^{-6} s) is becoming a common, if not exactly routine, possibility. A group at Cornell University (D. S. Klinger and A. C. Albrecht, *J. Chem. Phys.*, **53**, 4059; 1970) have now taken some important steps beyond the simple demonstration that such fast-decaying spectra can actually be seen by exploiting some of the unusual diagnostic techniques which have recently come into use in the more conventional time range.

Quite the most remarkable of these is the method of "photo-selection" whereby, using intense polarized sources, an oriented subset of molecules can be excited and their absorption spectra measured in the oriented condition, that is before rotational relaxation has time to be felt. This can be achieved without too much disturbance by illuminating the system in a polymer matrix and taking advantage of the high power and polarization of laser light. With sufficient intensity it is then possible to measure the direction of polarization of the emitted light in relation to the geometry of the molecule and to study the influence of chemical substituents on the dichroism as well as the wavelength pattern of the spectrum. (Although an advantage, laser techniques are not essential to photoselection; some impressive work with conventional sources has also just appeared—see, for example, T. G. Pavlopoulos, *Ber. Bunsenges. Phys. Chem.*, **74**, 989; 1970.)

In the nanosecond region none of this is easy; Klinger and Albrecht were forced to work at the very limits of time resolution, eliminating spurious fluorescence effects and concentrating on the anthracene derivatives which are well

known candidates for long lived excited states. Supplementing their recent announcement of the first ever observed singlet dichroism, in anthracene (*J. Chem. Phys.*, **50**, 4109; 1969), they have observed the change in the short-lived spectrum on methylation and have found significant new bands which show polarization in the direction of the substituent. This is adduced as evidence that the transition involves the methyl group in an essential way and must therefore imply the reorganization of σ rather than π electrons. The existence of such a low-lying σ transition would be a surprise to theoreticians, but quantum-mechanically it is not entirely out of the question. Meanwhile, the measured wavelength for transition to a second triplet state in anthracene itself gives an energy for this (4.74 eV) which agrees almost embarrassingly well with recent theoretical predictions (4.75 eV) (M. K. Orloff, *J. Chem. Phys.*, **47**, 235; 1967).

There are other surprises as byproducts

of this work. A strong isotope effect is observed on the lifetime of the excited 9-methyl anthracene, which cannot be a matter of selection rules and must point to a radiationless component in the decay mechanism. This would be worth a whole study in itself.

Clearly these results are only a beginning and will stimulate much further effort to obtain higher resolution and push measurements into the even shorter time scale where more problematic higher excited states can be expected to show up. What makes the whole field so interesting is that, by one of those powerful coincidences which mark only a few areas of research, both theoretical and experimental work seem to be straining towards similar answers with a roughly comparable degree of success. This, at least, should ensure that the study of nanosecond spectra will not fall into the dull taxonomy which tends to be associated with molecular spectroscopy on a more leisurely time scale.

Atmospheric Temperature from Scattered Laser Light

THE temperature and the ratio of aerosols in the troposphere can be measured by observing the frequency spectrum of the light scattered from a highly monochromatic laser beam. The frequency of the light undergoing Rayleigh scattering by molecules is Doppler shifted by thermal motions to produce a gaussian spectrum, the width of which depends on the temperature. Because the aerosols have much smaller random velocities, they produce a narrow spike at the peak of the molecular spectrum which can easily be identified. Winds will produce a frequency shift relative to the transmitted light and turbulence results in a broadening of the aerosol spectrum.

Fiocco and DeWolf (*J. Atmos. Sci.*, **25**, 488; 1968) were able to distinguish between aerosol and molecular scatter in a laboratory atmosphere, and now in work reported in next Monday's *Nature Physical Science*, Fiocco and his co-workers have improved the equipment and technique sufficiently to make possible its application to the troposphere. Light from an argon laser was directed upwards into the atmosphere and the backscattered light was collected by a mirror so that its spectrum could be analysed by an interferometer and photon counter. In order to study a defined height interval, the laser light was chopped to provide pulses and the receiver gated on after the appropriate time delay. The system thus operated as an optical radar. The temperature was obtained near the ground and at 4 km altitude, and the values agreed moderately well with the results of a balloon sounding some distance away. It seems that an accuracy of a few °C

is possible with Fiocco's equipment, but further studies of systematic and random errors are necessary.

The range of the apparatus could be improved by using a high power continuous laser or else a pulsed liquid or solid laser, and with some other modifications it should be possible to measure aerosol and molecular scattering to considerable heights in the atmosphere. It will be particularly valuable to obtain the aerosol/molecule scattering ratio at 30–40 km altitude, a region often used for the calibration of other optical radar experiments with the unproven assumption that the aerosol scattering is small (Kent and Wright, *J. Atmos. Terr. Phys.*, **32**, 917; 1970). Cometary and meteoric dust in the mesosphere might eventually be distinguished from molecules; this has been a matter of some controversy among the workers with optical radars who have hitherto not analysed the spectrum of their echoes. As a ground based probe for studying temperature and density in regions above the ceiling of routine balloon soundings (about 30 km), the technique might provide an economic alternative to rockets for studying stratospheric structure. This new technique for remote measurements of temperature, winds and aerosol content in the troposphere and lower stratosphere may be convenient for the research meteorologist if time and range resolution are improved. Furthermore, with such improved resolution, it may become feasible to make a direct measurement of the location and magnitude of the "clear air turbulence" which constitutes a potential hazard to high flying aircraft.

Higher Education in the 1970s

A conference on the future structure and curricula of higher education in Britain was held at Gonville and Caius College, Cambridge, on January 5-7 with the sponsorship of *Nature*. The report of the proceedings which follows, prepared by the staff of *Nature*, is intended to show the chief lines of argument and to suggest some of the problems which now call for attention.

EVERYBODY at the Cambridge conference rejects the Kingsley Amis view that "more means worse". The question is rather whether "more means different". The objective of the conference as a whole was to identify the pressures to which British higher education is exposed, to identify the responses of the system which are already apparent and to throw some light on the future course of events.

Sir Eric Ashby, the chairman of the conference, begins by saying that the universities are in a state of disequilibrium. They are subject to internal pressures from students and to external demands for manpower, yet they have an inner logic of their own. The goals of British universities must be reviewed and their inner logic, which rests on the beliefs of the academics, must be defined in the near future. Although it is the responsibility of government to meet the demand for places in higher education, the state is incompetent to determine the university's inner logic. Sir Eric thinks it significant that the thirteen proposals put forward by previous government for saving costs in the universities were all rejected by the vice-chancellors, but these in any case would only have touched the edges of the problem. Yet the universities have no suggestions to replace them. Similarly, most of the Cambridge colleges are against the proposals of Professor Brian Pippard but have few suggestions of their own for reshaping university courses.

Sir Eric considers that many of the problems that will be facing British universities in the coming years are already apparent, in the United States. Social pressures are forcing many students into the universities, and he suggests that one in six of them is there unwillingly. There is wide agreement about the folly of trying to resist the pressure of the demand for higher education, but Sir Alan Richmond believes that we should merely note the situation in the United States, for the social system there is very different from the British. But undoubtedly there must be changes for the benefit of the bulk of the students—the academically oriented students are more easily catered for.

Professor R. V. Jones raises the question whether the chief criterion for expanding higher education should be to increase the gross national product (GNP). Like many, he is suspicious of using manpower forecasting to determine the size of the university population and he says that it is not necessarily proven that more higher education will improve national living. He does not want to stop people having education after the age of eighteen but he wants to see a system of higher education in which the best students are not hampered by the less academically inclined.

Professor John Vaizey suspects that an expansion of higher education does not necessarily increase the gross national product. The correlation which can be seen in other countries is so slight that no argument for expansion can be based on this premise. He believes that a country as rich as Britain should educate its people by providing sufficient places for those who want them without restriction of the subjects studied. The crucial question, he says, is how do you reject potential students?

Will the traditional structure of British universities remain unchanged by the various pressures for expansion? In Vaizey's opinion, the so-called traditional structure no longer exists. Universities have changed very much in the past few years and the range of choices now open to students is very much greater than many people suggest.

Pressures on the Universities

Professor L. R. B. Elton singles out two particular pressures on the system of higher education. First, there is the considerable social pressure from those anxious to have a university education. Professor Elton believes that raising the entry requirements is an unrealistic solution to this problem. The second pressure, which Sir Eric Ashby had earlier described as suction, is the demand for manpower. Because it is almost impossible to produce accurate forecasts of manpower requirements, there is a clear need to provide a flexible education, yielding more generalists and fewer specialists and taking account of the inevitable and increasing swing to social occupations (but not necessarily social sciences) and the increasing requirement for graduate technicians (by which he means not only those in technical occupations, but also nurses and perhaps primary school teachers). Echoing Vaizey, Elton believes that because Britain is a rich country, higher education should be related not to what the country needs but to what potential students want. Moreover, the best features of the university tradition should be preserved.

Professor Elton is depressed about the traditional binary system of education dividing the universities from the polytechnics. He is sure that the majority of students are anxious for an academic education. They will in general enter the polytechnics only if the universities will not have them. What is to be done? Professor Elton lists five possibilities. First, the free market solution in which each institution competes through its own endeavours for a share in the

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overall expansion; rich though Britain may be, Elton doubts whether such a system can be supported. Second, the parallel solution, where the universities form a distinct elite and the bulk of the expansion takes place in the other institution of higher education. A third possibility is the multiversity, where all the institutions of tertiary education in a specific region are combined. A fourth solution is part-time study—which can provide more places at less cost, but which also entails that the less capable students are selected for a harder way of study. A fifth possibility described as the end-on solution, would interpose a system of junior colleges between the schools and universities. Whatever solution is finally adopted, it must be viable in the year 2000. Elton rejects the binary system because it imposes a choice on students at eighteen. He similarly dismisses the multiversity as unwieldy size and too dispersed. The logical alternative, he says, is the end-on or junior college system. Students would leave school at 16 or 17 to enter junior college where they would study for two to three years, achieving a diploma at the end of the course. This would cost little, for students could live at home and no research equipment would be required. At 19, the students could, with mature judgment, choose whether to go to university or not.

The Junior College Solution

This is the structure, but what of content? Elton sees a unit credit system of the type now in operation in the Open University as desirable. But whatever scheme is accepted, it must improve the educational chances firstly of boys from the working class and secondly of girls of all classes.

Professor Lilian Hawker offers as a small case-study in the multiversity the collaboration between the University of Bristol and the college of education there. There and elsewhere she thinks this kind of development may point the way to the multiversity. She is also anxious about some aspects of the junior college solution—for one thing, students will lose the feeling of excitement at going to university at eighteen. Dr George Tolley is no happier; from experience in the United States, he feels the junior colleges have no academic respectability and merely ape the universities. He sees a need for diversity in educational attainments which is neither met at present nor solved by adopting the junior college system. Elton argues that US junior colleges are not in the least end-on but in fact binary.

Dr R. J. Elliott suggests that the junior college system will merely delay entry into the binary system by three years. Sir Nevill Mott is curious about the kinds of teachers envisaged for junior colleges, but Elton sees that the gap may well be filled by the present staff of colleges of education and by sixth-form teachers. Dr Henry Nathan wonders whether what is being sought is a response not to increasing numbers but to increasing number of failures in which case, he says, only the United States can afford to educate "cool outs".

Professor Vaizey also argues that in spite of widespread attacks on university values, the universities are now better than ever before. Sir Alan Richmond agrees, and dissents from Elton's opinions about the reasons why students choose particular forms of higher education. At his own polytechnic, almost 50 per cent of the October intake had decided on a polytechnic education by July, well before university places could have been awarded. He says that the choice of institution depends less on prestige than on the character and quality of courses. Dr F. E. Jones is particularly interested in what influences a student to take a particular course and is worried that the universities have made no effort to find out what the users of graduates (that is, in the main, business and industry) want from universities.

Ashby agrees with Vaizey that there must be "good" and "bad" universities, but all university degrees are theoretically of a common standard (with internal examiners as guarantors), so that the question is to decide whether high quality

and low quality degrees are to be created in the same university or in separate systems. He is also concerned about the relationship between research and teaching, and in particular with the impolite question of how much poor research has to be undertaken to sustain the high-powered research which is the basis for the scientific reputation of a department.

Mr Derek Oldfield complains that the discussion is biased towards the problems of teaching science. He notes that student opinion must be a factor in any decision on higher education—student opinion at the University of Sussex, for example, was that the government should not be allowed to get away with the illusion of solving the problems with its thirteen proposals for university economies. Mr J. S. Morrison says that it is inevitable that decisions will have to be taken about which universities should achieve excellence in which subjects. There is simply not enough money for all 44 universities to reach the top class in all subjects. Mott replies that it is not a question of good and bad universities but of good and bad departments. He also raises the question whether every academic should continue research until retiring age. There is a clear need, he says, for incentives to persuade people from research into teaching.

Higher Education and the Economy

Sir Derman Christopherson feels that the financial problems have been greatly exaggerated. With good management and existing buildings, he sees no reason why, on the basis of a 2½ per cent per year increase in real budgets, the universities should not expand their student population by 5 per cent per year for ten years. In other words, there need be no disproportionate increase in the share of public funds devoted to the universities in the next ten years; beyond that, the picture is less clear.

There is some agreement that a diversity of sources of funds is bound to be a valuable safeguard. Christopherson agrees that there would be some value in an increase of student fees at universities to a larger proportion than at present of their true cost.

Dr F. E. Jones is less sanguine about money which has to be provided at the expense of other public services. The British economy has been stagnating since the turn of the century. With an increase in GNP of 2½ per cent per annum, how can Britain possibly hope to pay for hospitals, social services and then the expansion of higher education? Britain is too lethargic, he says; if other countries can manage 6 per cent a year, so should Britain. The trouble seems to be that education is not coupled to the GNP.

Nathan is not sure what contribution higher education can make to the GNP, but feels that it plays a worthy part in the redistribution of income. Vaizey also disagrees with Jones. With increasing affluence, it is to be expected that the proportions of the GNP being spent on food and housing should be decreased, and that more should be spent on higher education. How this is paid for, he thinks, is unimportant; unless there is a radical break in the history of Europe in the twentieth century, these people will be provided for. Mr R. A. Becher also justifies what Jones has said by pointing out that just as students are today asking for specific courses, so in the future they are going to create the kinds of jobs they want to do.

Polytechnics and the Binary System

What purpose were the polytechnics meant to serve and how will they coexist with the universities? Becher suggests that Mr Anthony Crosland put forward the proposal for the binary system because the universities are too elitist, irrelevant to national needs and too expensive. But Ashby disagrees. He believes that the binary system was created to prevent a landslide with other colleges wanting university status. He also suggests that the assumption that the poly-

technics are cheaper is not necessarily proven. Richmond agrees that the method of financing the universities is so different from financing in the local education sector that costs cannot be compared.

Vaizey has other suggestions. He believes that the binary system was established because the administrative problems of the UGC were such that it would collapse if it were given a wider sphere of responsibility. He says that the government was also worried about the costs of university education and of providing residence for students in traditional universities. He suggests that the situation is now changed and the reasons for the existence of the binary system no longer apply.

As far as the relationships between polytechnics and universities are concerned, Richmond believes that there will be no change in the binary system unless the universities themselves are prepared for quite radical changes. A unitary system of higher education will be possible, he suggests, only if the universities are prepared to give the same status to part-time and non-degree students as to other undergraduates. The binary system has hardened, he says, because when the colleges of advanced technology were given university status, they shed their Higher National Certificate and other courses to become more like the established universities.

Mr George Tolley agrees and he also draws attention to the position of the colleges of education. These institutions, he suggests, must become multi-purpose and possibly establish links with the polytechnics. They should also look for an upgrading of the whole process by which they operate and should not deal only with courses designed for low level occupations.

Vaizey suggests that the universities are not in favour of a unitary system because university staff would be outvoted by staff from other institutions, and they would also be afraid that the special facilities of the universities—for example, libraries—would be flooded by other students. Elton also believes that differences in salary scales in polytechnics and universities present difficulties in the interchange of staff between institutions, and Dr Dilys Hill suggests that even if the universities were willing to change for the sake of a unitary system, they could not do so quickly enough.

Professor Michael Pentz believes that everybody who is capable of benefiting from higher education should receive it and he points out that the Open University was founded chiefly on this premise. Its students are at present over the age of 25 and they have missed out in one way or another. What can the Open University contribute to the expansion of higher education, can it in any case cope with the 18–21 age group? Pentz suggests that the first thing is to see whether the Open University works for the people for whom it is designed and then to look at its possibilities for other age groups. But if the Open University can cope with 18 year olds, Pentz points out that it would be able to do so at very low cost. He would be unhappy if the updating and in-service courses planned for the Open University were dropped to enable it to cater for 18 year olds.

Two-year General Courses

What of structural changes in the universities? According to Professor Brian Pippard, British universities are failing to carry out the duty imposed upon them by society. The extra money which is being made available to higher education has been used by academics to maintain their own way of life without too much regard for the national consequences. He suggests that there has been no increase in the past few years in the number of jobs which require a highly specialized education and that there is already over-production of physics and chemistry graduates and of PhD graduates in engineering. A way out of this situation is to change the pattern of undergraduate degree courses in such a way that all students will take a general course for the first two years, after which only those who want and are

capable of taking specialist studies should carry on for a further two years. This system embodies the concept of the "educational age of consent". Pippard says that the present system means that students are selected for higher education at the age of eighteen and that the competition for university places puts many constraints on the schools and he believes that the best way of remedying this situation is to abolish selection at 18+.

The system which Pippard is proposing would mean that students would be selected at the age of 20+, but he believes that the student himself should be able to decide whether or not he wishes to go on to more specialist studies. This he believes is the realistic educational age of consent. The sort of idea he has in mind is that students should be offered a choice of between 15 and 20 organized courses including economic, legal and social issues and techniques useful for making decisions. The two-year course should be divided roughly into two-thirds general studies and one-third specialist education. During this course, students would be able to discover whether they want to proceed to a more specialized education and they would only be allowed to do so if they complete the two-year generalist course successfully.

Will such a generalist course save money? Although Pippard points out that his ideas were formulated chiefly for educational reasons, he believes that they have advantages in cost saving compared with the present system. A fundamental part of his suggestion is that not every university would build up specialist teaching and research facilities in every subject. There should be even greater concentration of resources in particular fields of study. He points out, for example, that the staff:student ratio in disciplines such as biology and oriental studies is much greater than in many other fields. He envisages that his proposals would require that a staff:student ratio of about 15:1 should be established for the two-year generalist course and of about 8:1 for the specialist course. Such a concentration of resources and the subsequent change in the staff:student ratio, he calculates would result in a saving in unit costs of between 30 and 35 per cent without a decrease in the quality of graduates produced.

There should be no increase in the amount of money for research. Pippard says that there are not enough ideas to support a greater scale of research activities and in any case he points out that concentrating resources into big departments engaged on advanced research work would not necessarily require greater research expenditure.

'Pippardism' Debated

Dr Sydney Brenner says that the danger is that of teaching about science rather than teaching science itself. Even the present undergraduate studies do not produce good scientists, and the two-year generalist course would be useless for those who are academically inclined. He is not, however, entirely opposed to general degrees. A three-year general degree may be feasible and he also suggests that the time has come to decide that some sciences, for example microbiology and even biochemistry, should not be taught at the undergraduate level.

Elton is in full agreement with Pippard's concept of the educational age of consent but he is dubious about the practical possibility of introducing generalist courses. More evidence is required to show that those generalist courses that have already been established—for example, the one-year foundation course at Keele—fulfil their objectives and he points out that there is no experience of generalist teaching on a large scale. He also disagrees that Pippard's proposals will necessarily increase the staff:student ratio because the generalist courses would require teaching by discussion groups and this is particularly heavy on staff time.

Dr F. E. Jones likes Pippard's scheme. Pointing out that it is easy to recruit graduates into research but difficult to

accept science graduates in marketing and other fields without retraining, he says that there will be a good market for graduates with a more general university training. Such graduates would be no worse than those from the present stereotyped courses.

Morrison can see some difficulties in teaching courses at a university which does not have specialist facilities in certain subjects. Hill takes this idea one stage further and suggests that some universities will inevitably become liberal arts colleges. Pippard accepts this possibility but believes that it is possible for a university to have a specialist group researching on, for example, solid state physics and still able to offer a general course in physics. But Hawker disagrees. She believes that good geneticists would not be willing to work in isolation from other biologists.

One of the weakest points in Pippard's proposals in Elton's opinion is that students not accepted for specialist studies would effectively be barred from further university education at the end of their two-year generalist course. He says it is inevitable that students will opt for specialist studies and he suggests that a further two years of education should be open to generalist students. Becher agrees that those students who want to stay on should be given a choice of studies, but he says that the structure proposed by Pippard is monolithic. He believes that it is likely to create a bottleneck at 20+ and that this will cramp a student's education up to that age just as the bottleneck at 18+ is now cramping education in secondary schools.

Would Pippard's suggestions for university science curricula be feasible for the arts and humanities? Hill believes not. A similar scheme which was put forward at Southampton for six years of study in chemistry, the first two leading to a general degree, the second to an MPhil and the last two to a PhD, would not apply in the social sciences and humanities. Oldfield agrees and he says that in the arts more than two years of study would be required for a unification of knowledge. That, says Pippard, is nonsense. Three years of study has been regarded as sacrosanct for too long and if academics were suddenly told that they must give two-year courses, they would soon be able to do so.

University staff must interest themselves more in teaching if Pippard's ideas are to have a chance of working, Christopherson suggests. This implies that teaching must be more prestigious and attractive but he is not sure that this can be accomplished by offering generalist courses. In any case, it seems that different patterns would have to be established for science and other courses. The division between arts and science students is already bad enough without further differences being created. Christopherson also says that it is already difficult to get students to leave universities and he foresees that about 80 per cent of the students who complete a two-year generalist course would want to stay on and specialize. This necessarily means that many would have to be discarded.

Rationalization of Resources

As far as rationalization of resources is concerned, Christopherson sees grave problems. Departments in some universities would have to be shut down and such a situation could not be forced upon the universities unless they lose some of their individual autonomy. Does this mean that universities should sacrifice their autonomy and replace it by collective autonomy of the whole university system? But Sir Frederick Dainton sees rationalization of resources as a product of selective growth rather than selective termination.

In arts subjects, Morrison says that more means more and not necessarily different. If the choice is between the number of students at universities or putting students through more quickly, he would choose the latter. He would certainly not want to select students for university education and then turn them away after two years. Pippard's

suggestions have some merit, Morrison suggests, but a more viable solution may be to teach for four terms a year for two years or even to give students course credits and let them resume their studies after a period away from the university.

Kemmer says that the thinking about academically inclined students should be separated from suggestions for the bulk of university courses. He advocates a system of unit courses which are much more rigorous and more specialist than in ordinary degree studies. Such unit courses would not be tied to a particular year of study and would only appeal to those students who would become future academics. Qualifications for entry to PhD studies should be based on successful completion of these courses, Kemmer suggests.

Discussion of more general university courses, in Sir George Pickering's opinion, dodges the issue. The education process is continuous and he believes that consideration of education at school separately from that at university bypasses many of the problems. What happens in the university has a profound effect on the situation in the schools and Pickering is appalled that a choice between arts and sciences should be forced upon a student at the age of 15. He believes that people who have studied a specialism since the age of 15 at school and for four years at university will be ignorant when they leave the formal education process. He lays the blame for this situation at the door of the universities because they assume that their function is to train scholars, that the undergraduate course should last for three years and that education stops at graduation. He points out, for example, that the real skills in medicine are acquired only after graduation.

Mr William van Straubenzeel is depressed about the number of students who reach universities by a sort of escalator. He sees value in spending a year between school and university because this would give students an opportunity to reflect on their future education and it might lead to some easing in the demand. But such a year out of the education process should be entirely voluntary. There are, however, a few incentives which could be offered. One of the chief irritants in the grants system is that students are financially dependent on their parents and van Straubenzeel suggests that if grants were assessed not on parental income but on the student's own income, this could be an incentive for spending a year out of the academic process immediately after leaving school.

Problems of Colleges of Education

Mrs Shirley Williams observes that the proportion of the GNP earmarked for higher education in Britain is large and that nobody of whatever political leaning is of the opinion that the share going to higher education should rise greatly. She also thinks that to swamp the polytechnics before they have the chance to establish their own autonomy would be to risk repeating the disastrous experience of the CATS and the BED. It seems to her a pity that the colleges of education have been so neglected. The result is that they are now anachronistic monotechnics which offer no possibilities for growth but which are difficult to remove. Dainton disagrees; he thinks that the colleges of education offer a kind of participatory student education which is preferable to that provided by many of the poorer universities. Why, he asks, cannot they be linked to the universities to teach a wider range of courses? They are fast becoming a cultural deprived section of the community. A pitifully small proportion of each year's intake have A-level qualifications in science subjects.

Dainton thinks the question is to consider science teaching in the broader context. He is left with the impression that the hard work must be done in the university department. Dainton closes by suggesting one solution. He thinks that a ferment must be initiated with the universities and that the pot must be kept on the boil. Only in this way can the necessary changes be accomplished.

Dowsing Experiments

by
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Experiments organized by the British Army and Ministry of Defence suggest that results obtained by dowsing are no more reliable than a series of guesses.

HISTORICALLY the practice of dowsing goes back many centuries. The most ancient reference is a Chinese engraving of AD 147 showing the Emperor Yu holding a forked divining rod. In the sixteenth century divining rods were used by miners searching for metal ores although this practice was condemned by Luther. By the seventeenth century various theories to explain the phenomena were put forward by several writers but with a lamentable lack of evidence of any systematic trials to substantiate the theories.

In the present century the subject has received some publicity and there are national societies of dowsers. From time to time dowsing is mentioned in the press¹ and recently trials were featured in a television programme (Margins of the Mind on Granada TV, in May 1968). Many people claim the ability to locate water, metals, stoneware, archaeological remains and other buried objects by dowsing. Some go so far as to claim the location of these objects by dowsing over a map of the area without the necessity of going over the ground.

Three types of apparatus are commonly used: (1) forked rods; (2) a pair of L shaped rods, and (3) a pendulum or plumb line. When one considers these three methods and the wide variety of objects which it is claimed can be found by dowsing, it is clear that to discover a satisfactory scientific or physiological explanation is a formidable task. Some writers claim that the subject is not susceptible to scientific analysis but belongs to the realm of art, appreciation and subjective judgments.

Before seeking explanations, it is necessary to substantiate the claims. For this purpose, a series of trials were devised at the Military Engineering Experimental Establishment (MEXE) of the Ministry of Defence, to test the validity of dowsing in a controlled series of experiments. These covered map dowsing and *in situ* dowsing for buried mines. Later tests were carried out for water divining by the Royal School of Military Engineering (RSME). Some additional trials were devised to test theories put forward.

Map Dowsing

An accurate survey was made of one of MEXE's outstations and a map at a scale of 1/2,500 was prepared. The area covered 384 acres and contained 6.7 miles of roads and tracks. To make the trial manageable twenty inert mines were buried only in the roads and tracks.

The map plus a sample mine was sent to experimenter A because it was reasonable to suppose he should know what he was looking for. He was told that an unspecified number of these mines were buried only in the roads and tracks and that any of his marks would be assumed to cover the full width of the road and a strip 10 feet wide. This corresponds to an error of about ± 0.025 inches on the map.

Experimenter A asked for time and practice. His first attempt gave twenty-seven mines and none of them nearer than 80 feet. He then asked for more sample mines to practise on, and that he should be given the position of two of the buried mines, and further that a short stretch of road containing some mines should be indicated. This was done and a marked portion on the map, 3,400 feet long containing five mines, was selected. His results gave eight mines in this stretch with the nearest mark 20 feet from a mine. In spite of these discouraging results he suggested a more limited trial. A plan of a figure of eight track at a scale of 1/480 was sent to him with a short stretch 300 feet long indicated, in which was buried a row of five mines. This map was used by experimenter A and four others, with the result shown in Table 1.

Table 1 Achievements on Figure of Eight Track

Experimenter	Distance mark to mine (feet)
A	149
B	159
C	150
D	102
E	84

A mark midway could not have been more than 150 feet from any possible position.

Experimenter F was given the original map in the same conditions. He asked for a sample of the inert mine filling (sand and pitch) which he was given. His first trial gave twenty-six mines, the nearest mark being 60 feet from a mine. He then suggested that the filling was too similar to the surrounding soil and asked to try with something radically different. He therefore sent a bottle of homeopathic medicine and this was buried in one of the roads. He failed to locate this on his second trial.

Experimenter G was also given the map and the same conditions, but was told that there were fewer than fifty mines. His result gave fifty-three mines and the nearest was 40 feet from an actual mine.

During these trials a limited guessing exercise was carried out using the staff at MEXE. Fifty members were asked to guess the number and locations of mines in the 3,400 feet stretch of road. Eighteen guessed the correct number and one of these was within 1 foot of a mine.

It is easy to show that none of the results are better than pure chance. Taking A's first results, his nearest mark is within 80 feet of a mine. The whole 6.7 miles can be thought of as units 160 feet long, that is mine ± 80 feet. There are therefore 221 such units and with twenty mines and twenty-seven marks on the dowsers' map one would expect $20 \times 27/221$ or about 2.5 answers within 80 feet. Only one was achieved, a below chance result due to the grouping of his marks in a few areas. Similar calculations for other dowsers give similar results.

To sum up on map dowsing, the results from all the trials are really failures and there is no evidence that this is a practical method for locating mines. Most experimenters claim that their marks are either "spot on" or else failures. None of the experimenters achieved better results than the guessing exercise. It may be said that because only seven dowsers have been tested, the results are too few to disprove the claims.

In Situ Dowsing

In this test several mines were buried in a grid pattern and experimenters were asked to dowse over the places where mines were buried and over others where they were not. Using χ^2 tests it is possible to determine whether the dowsers are performing better than chance.

It became clear that the test could also be used to widen the inquiry and determine the dowsers' ability to distinguish between different types of buried objects. Five classes were established: M, metallic mine; P, plastic mine; C, concrete block; W, wooden block; B, blank or nothing. The concrete and wooden blocks were the same size and shape as the metallic mines.

Next a decision was made on the spacing and numbers of these objects. It was felt that 20 foot centres would be far enough apart to eradicate the "influence" of one object on another and all the dowsers agreed with this condition. The number of objects determines the significance level and power function of the experiment. Because the number of dowsers was not expected to be large a significance level of 1% was

chosen. This means that there is a 1% chance of falsely detecting an association. The power function considers the different analyses of the results and the smallest association, say, between metal and plastic mines, must have enough figures in it for detectable differences. On this basis the total sample size was fixed at 400, that is, five groups of eighty of each class.

An area of land consisting of heath and heather was marked out and half of it was cleared and raked level. Each half had 200 squares and the objects were buried in a random pattern as shown in Fig. 1. Holes were dug at the centres of every square and different gangs of men buried each class of object so that no one could know the localities of all 400. None of these men took any subsequent part in the trials nor were they present on the site during trials. The only master location plan was locked in a safe throughout the experiment.

Response score cards were provided for all dowsers, who were not told of the wooden and concrete objects but were shown the mines. They were asked to dowse in front of small wooden pegs carrying the square identity and to record mine, plastic mine or nothing. Neither of the two people who

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	
20	2	4	3	1	4	1	4	3	2	1	2	4	3	2	5	4	4	5	1	5	20
19	6	3	1	5	1	2	4	5	6	3	1	5	1	4	3	4	6	2	6	3	19
18	5	1	6	1	3	1	4	3	2	5	1	3	4	3	1	1	4	5	2	5	18
17	2	3	1	2	1	4	6	3	1	2	3	1	5	1	2	2	6	1	6	3	17
16	2	5	6	3	5	1	4	2	4	1	4	2	1	6	1	2	3	5	1	6	16
15	4	2	3	6	1	4	2	5	2	4	6	1	3	1	4	1	2	3	5	3	15
14	6	1	1	3	5	3	1	2	4	2	1	4	1	2	1	6	4	1	2	2	14
13	6	2	3	1	2	2	2	1	2	3	3	4	5	1	4	4	4	5	4	1	13
12	3	4	5	3	6	3	3	2	6	2	5	2	3	6	2	1	6	4	2	4	12
11	4	1	3	4	3	1	3	4	3	1	1	3	1	3	3	3	4	3	4	2	11
10	3	4	1	3	2	3	1	4	2	5	3	4	2	1	5	5	1	4	3	4	10
9	1	3	3	4	3	2	2	1	4	6	2	3	4	6	2	6	2	1	5	4	9
8	4	2	4	5	4	5	4	1	5	6	5	1	1	3	1	4	4	2	1	2	8
7	2	1	1	3	6	4	2	4	4	3	3	2	3	6	2	1	3	4	6	4	7
6	3	4	3	6	4	3	4	2	1	5	5	4	3	2	3	5	3	1	2	6	6
5	1	2	2	2	1	4	3	4	6	3	1	6	4	3	4	3	6	2	4	4	5
4	6	3	6	1	4	2	3	6	2	1	4	2	3	1	3	6	4	2	1	2	4
3	2	5	4	5	5	1	4	1	4	4	2	5	1	3	2	3	2	3	2	3	3
2	6	4	6	2	4	3	2	5	3	2	1	3	2	4	2	6	1	2	5	2	2
1	1	5	3	5	1	4	1	2	1	2	3	1	4	1	3	2	2	6	2	4	1

 PLASTIC MINE

 PLASTIC BAR MINE

 CONCRETE DUMMY

 METALLIC MINE

 WOOD DUMMY

 BLANK

Fig. 1 Random number table for mines.

Table 2 Response Table

Response	B	M	C	W	P	Totals
M	8	7	8	11	7	41
P	21	26	24	22	26	119
B	11	7	8	7	7	40
	40	40	40	40	40	200

The second row shows the number of times the dowser said metallic mine and the columns indicate how many of these responses fell on the objects B, M, C, W or P. The only correct score for line 1 is under column M, for line 2 under column P and so on.

supervised the laying took any part or were anywhere near the site. The number of each class of object was fixed at forty each in the natural and in the raked ground, which gives a response table for each dowser. A typical set of responses is shown in Table 2.

Twenty-two people volunteered to try their powers. Nearly all were firmly convinced they could do it. One person, at his own request, asked to repeat the trial because he felt (subjectively) that he had not done very well at his first try. One

**Fig. 2** Dowsing with forked rods.**Fig. 3** Dowsing with two L shaped rods.

other was asked to repeat the trial because his score card had ambiguous markings.

Two of the methods used are shown in Figs. 2 and 3. Dowsing rods were of many varieties including wood or nylon and each dowser was free to use whatever method he chose. One dowser used a plumb bob.

The responses can be analysed in a great many ways. For the purpose of these trials they were grouped as follows: (a) total response in a 2 by 3 by 5 table for raked and natural ground; (b) response mine versus not mine, that is (M+P) versus (B+C+W) 2 × 2 table; (c) response object versus blank, that is (M+P+C+W) versus B 2 × 2 table; (d) response mine versus blank (M+P) versus B 2 × 2 table; (e) $\Sigma\chi^2$ for a, b, c and d for each experimenter; (f) $\Sigma\chi^2$ for all experimenters.

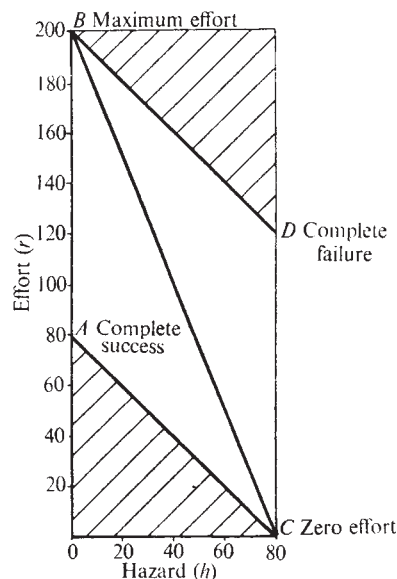
While this analysis was being made it was clear that the simple mathematical treatment did not reveal the whole truth. Thus in a simple 2 × 2 table, for example (M+P) versus (B+C+W), there is one degree of freedom. Thus if we assume r "yes" responses we have Table 3.

Table 3 Responses after Mathematical Treatment

Response	(M+P)	(B+C+W)	Total
Yes	$80-h$	$h+r-80$	r
No	h	$200-r-h$	$200-r$
	80	120	200

Only one further figure, h , is needed to complete the table. The χ^2 test does not distinguish between a good and a bad result. Thus if it is assumed that $r=100$ (reasonable average) and $h=20$ or 60, then $\chi^2=33.3$ each time. The second result is much worse than the first because the dowser has only located twenty mines out of eighty, whereas in the first result he located sixty. Thus the χ^2 tests do not distinguish between good and bad dowsers and to overcome this objection the following method was devised. Clearly the dowser who responded "yes" to every square would find all the mines, but at a cost of maximum effort in digging up every square. The dowser who responds "yes" at all the B+C+W places would achieve total failure but with far less effort.

There are thus two aspects to consider—effort and hazard. Effort is the number of squares to be dug up, that is, the number of "yes" responses, and hazard is the number of mines not discovered. This leads to a two-dimensional plot of effort against hazard (Fig. 4).

**Fig. 4** Effort and hazard.

At the point 80, 0 is complete success; at 200, 0 is maximum effort and all mines found; at 120, 80 is complete failure and no mines are found; at 0, 80 is zero effort and no mines are found. The results all lie within the parallels given and pure chance results lie on the diagonal line as shown. About this diagonal line probability points can be calculated such that the probability of a score mark being beyond the point is $(1 - \text{confidence})$

Table 4 Mines Missed (Hazard), Holes Dug (Effort)

Experimenter	Raked		Natural		Total	
	Mines missed (h)	Holes dug (r)	Mines missed (h)	Holes dug (r)	Mines missed (h)	Holes dug (r)
1	—	—	33	126	—	—
2	22	136	14	160	36	296
3	75	20	67	22	142	42
4	—	—	23	139	—	—
5	33	104	65	51	98	155
6	50	64	46	53	96	117
7	49	70	61	43	110	113
8	46	79	31	111	77	190
9	7	158	6	174	13	332
10	12	177	4	189	16	366
11	36	100	53	73	89	173
12	23	121	—	—	—	—
13	27	113	34	108	61	221
14	21	136	42	102	63	238
15*	—	—	12	12	—	—
16	46	96	—	—	—	—
17	22	149	—	—	—	—
18	37	100	—	—	—	—
19	24	151	21	144	45	295
20	52	64	—	—	—	—
21*	—	—	27	37	—	—
22*	—	—	11	36	—	—
Mines present	80		80		160	

* Note that in these cases only part of the course was covered, so these results are not plotted in Figs. 5 and 6.

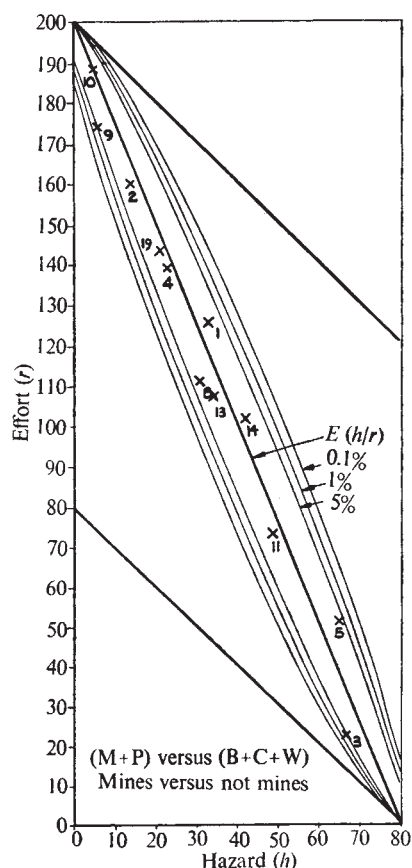


Fig. 5 Hazard and effort, natural ground.

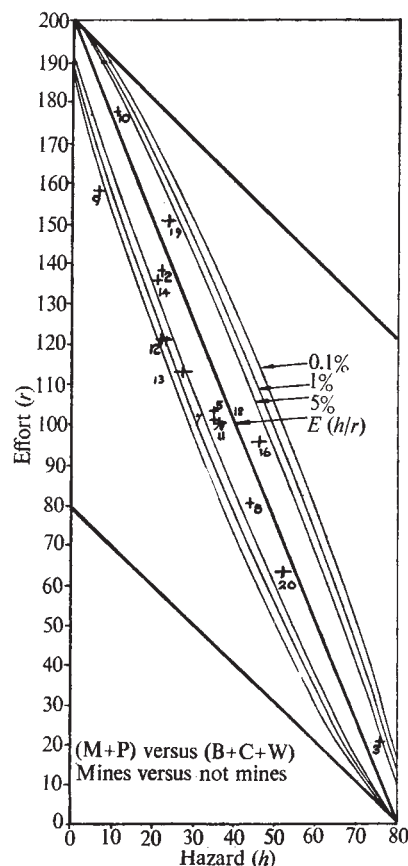


Fig. 6 Hazard and effort, raked ground.

level). Curves for 5%, 1% and 0.1% are shown. The further the score marks are from the diagonal the better is the performance of the dowser, and of course the marks must be tending towards point A.

Table 4 shows all the results for the twenty-two experimenters and these are plotted on Fig. 5 for the natural ground and on Fig. 6 for the raked. On the whole it is clear that most of the plotted marks are very close to the diagonal line of pure chance. Various other analyses were carried out but in no cases were the results good enough to excite interest. The best dowser was No. 9 on raked ground whose result was significant at the 1% level. This was, however, only achieved with a very high effort in digging many holes not containing mines. The results reveal a detectable difference between dowsing over raked and natural ground, which suggests that visual evidence in the raked ground helps the dowser. The effect of a few tell-tale signs would be to slide the diagonal line of Fig. 4 to the left because hazard and effort are both reduced by the number of such signs. The plotted marks then fall on the revised chance level diagonal. If the dowsers had to search for mines instead of trying over selected points it seems unlikely that they would have been more successful.

Water Dowsing

In the search for water, dowsing is more familiar than in seeking for metals or archaeological remains. In general, dowsers claim to find moving water—springs, pipes and so on—rather than static pools of underground water.

A test of the ability to detect flowing water was arranged with the cooperation of an experienced dowser. A 2 inch polythene pipe carried the water under a lawn and was controlled by a stopcock which the dowser could not see. He was asked to say whether or not the water was flowing in a series of twenty-five trials, the stopcock being on or off in a pre-arranged random sequence. He used a V shaped rod (rose cuttings) and walked across the line of the pipe to give his verdict. Two sequences were carried out giving fifty results.

The water was flowing in twenty-five of these. The dowser was correct in nine cases of water flowing and in sixteen of it not flowing, that is, he was correct in twenty-five out of fifty cases. This is entirely consistent with chance (guessing) and shows no evidence of being able to detect flowing water.

Further tests were carried out by RSME at Chatham. An experienced dowser undertook to train junior officers and judge their ability as dowsers. He took each of them over an alleged subterranean water flow when the student held one end of a forked rod and the dowser held the other. Students were then asked to dowse over what was alleged to be a second flow. Many officers were tested and 25% were judged to be highly sensitive. These tests were later found to be invalid because a boring at the first trial site found no water at all.

In an additional test, the 25 per cent of sensitive officers were asked to locate and estimate the depth and rate of flow of water within a given 12 yard square. The flow was known to be 80,000 gallons per hour through a 42 inch main 8 feet down. Forty-seven per cent were said to have "high" sensitivity and 20 per cent to have "nil" sensitivity and this cast doubts on their initial high grading.

Finally, the four most successful students were asked to dowse over an area 150 feet square containing several 6 inch water pipes, with flowing water about 4 feet down. The position was known but could not be seen on the ground. Eighty markers were put down at least 10 feet apart; sixteen of them were over pipes in an overall random pattern. The four students had to say which of the markers was over a pipe. An analysis of the results showed no significant difference for chance except for one student who differed by 5 per cent which might be attributed to an ability to dowse. The sample size is, however, rather small to derive valid results.

The result of all these trials was frankly disappointing, the students were inconsistent and the judgment of the experienced dowser proved to be faulty. There is no real evidence of any dowsing ability which could produce results better than chance or guessing.

Theories of Dowsing

Rocard claims that dowsers are sensitive to variations in the Earth's magnetic field². In most places the field is sensibly constant and therefore not detectable. But by dowsing in an aeroplane one is moving so much faster that these variations can be detected. Thus dowsing from an overbridge with vehicles passing beneath will, in Rocard's opinion, produce a result.

Rocard describes measurement of electrical potential differences between buried electrodes, and associates these with electrical currents and hence magnetic fields. These are in turn related to the flows of water through gravel dikes and seepages into wells when pumping water. By fitting small, light permanent magnets to the crooks of the elbows he found that his dowsers lost their ability. He therefore concludes that the organ of sensitivity is in the elbow and not in the head or hand.

Very few scientific tests are described and then only in relation to artificial magnetic fields. A rectangular wire wound frame

was set up to give a field between 0.3 and 10.0 mGauss at the body of the dowser as he walked past. A preliminary "weigh in" was allowed in which the dowser was told whether the current was on or off. In a series of five attempts after this 100% success was achieved. When the preliminary "weigh in" was omitted the result was pure chance in up to fifty trials.

This theory was tested at MEXE. Two coils were set up and an experienced dowser attempted to say whether the current was on or off. The field strength was 6.7 mOe 1 m from the plane of the coil. Three test runs of twenty-five each were carried out consisting of: (a) passing the coils placed in line 3 m apart; (b) passing between the coils 3 m apart with magnetic fields in line; (c) as for (b) but coils 1 m apart.

Results are summarized in Table 5. These results are no different from pure chance and show that this experienced dowser is not susceptible to magnetic effects.

During the MEXE trials it was suggested that the cause of the dowsers' signal was an alteration in the electrical properties of the skin, and an instrument was produced in which this difference could be measured. This consisted of two coils of wire protected by conducting rubber. The coils were loops wrapped round the hands so that they and the dowsing rods were held together. Screened leads connected the coils to a millivoltmeter arranged to read from -50 to +50. The loops had remarkable sensitivity, for by squeezing them almost any reading could be obtained. The inventor claimed the instrument measured capacitance or alternatively "radiaesthesia" which are unspecific waves of radiation.

The most successful dowser (No. 9) agreed to try the instrument over two rows of twenty squares. On the first row he was correct seven times, reading -50 to +40 when correct, and on the second row he was correct six times, reading -15 to -30 when correct and -5 to +50 when wrong. There was thus no correlation between instrument readings and correct or incorrect dowsing finds.

During the trials I carefully watched several dowsers at work (Figs. 2 and 3). With all methods quite small movements of the hand produce very large movements of the divining instrument. The problem with the common V rods is three dimensional and not easily apparent. Fig. 7 is an isometric sketch of the normal V rods. OX and OY are horizontal axes and the action of the dowsers' hands is to hold the rods in the position shown. This he does by first pulling them apart and then bending the ends by a torque about the vertical axes through A and B. Because the rods are small there is very little torque that can be resisted about the horizontal axes OX. If this is now treated as a structural instability problem it can be shown that, if the tip C is slightly displaced, instability will occur unless a considerable restoring torque can be applied about the XX axes. The rods will move violently and rapidly into the vertical plane.

The L shaped rods are held with the short leg vertical. Here again very little torque can be applied about the vertical

Table 5 Test for Magnetic Effects

Test	Response	Current on	Current off	Total
(a)	yes	8	4	12
	no	5	8	13
		13	12	25
(b)	yes	5	4	9
	no	8	8	16
		13	12	25
(c)	yes	4	6	10
	no	9	6	15
		13	12	25

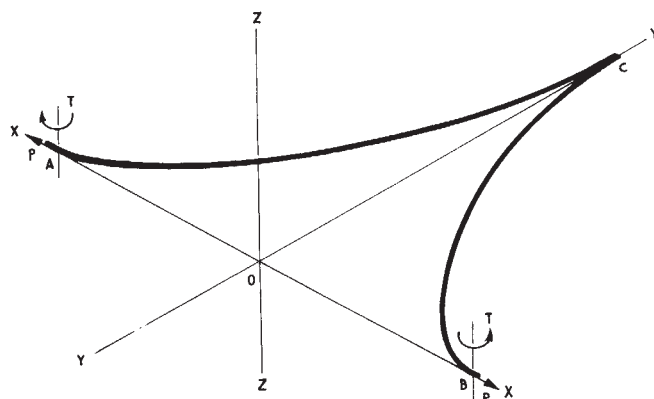


Fig. 7 Isometric sketch of V shaped rods.

axes except by gripping. In the instrument known as the "revealer" this grip is eliminated by mounting the short leg in ball bearings. If the short leg departs slightly from the vertical the rods are bound to swing. Because humans are right and left handed there is a tendency for the two hands to move in opposite senses either slightly inwards or slightly outwards. Possibly an inwards movement is easier and more natural so the rods move together.

In both cases, V or L rods, only extremely slight and imperceptible movements of the hands are required for quite large and spectacular movements of the divining rods because of the initial structurally unstable position chosen. This is most noticeable in the V rods and once they start to move they almost seem to become alive in the hands. I think that this is the explanation for a large part of the mystery surrounding dowsing.

Nevertheless, dowsers will continue to maintain their claims and to say that scientists dismiss their powers almost out of prejudice. The following arguments are often put forward³. (1) The "one good case" argument, that even one success is enough to prove dowsing. This is not statistically true. (2) The "test of time" argument that because dowsing has gone on for so long it must be true. This would also make witchcraft and astrology true. (3) The "core of truth" argument; that is, evidence from case after case. Compare old

Chinese saying "if a thousand people believe a foolish thing, it is still a foolish thing". (4) The "testimonial" argument that some famous men (Nobel prize winners) have endorsed dowsing. Even more, however, have pronounced against it. (5) The "good and bad dowser" argument that dowsing gets a bad name because too many amateurs have dabbled in it. That was not true in the trials described here, for only those who claimed to be good dowsers and were recognized as such by other dowsers took part. (6) The "unfairness" and artificiality argument. Usually this is a *post hoc* argument. Great care was taken in all trials to ensure that dowsers agreed beforehand that the test was a fair one. (7) The "unfavourable atmosphere" argument that the dowser is surrounded by disbelievers or those who want him to fail. This is not true, and I would have been delighted to find even one dowser with significant results. (8) The "persecution" argument—look what happened to Galileo. Dowsing has nothing to do with Galileo and is valid or not irrespective of what happened to him or any other persecuted individual.

¹ *Sci. J.* (November, 1967); *New York Times* (October 13, 1967); *Times* (December 11, 1967); *Sunday Express* (March 3, 1968); *Times* (March 5, 1968), *Engineering News Record* (May 2, 1968).

² Rocard, Y., *Le Signal de Sourcier* (Dunod, Paris).

³ Voigt, E. Z., and Hyman, R., *Water Witching* (University of Chicago Press).

L-Asparaginase and Human Malignant Disease

by

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The enzyme L-asparaginase, which breaks down asparagine, causes certain tumours to regress. This property has been put to use in the treatment of malignant disease in man.

THE discovery that L-asparaginase has a useful place in the treatment of some forms of malignant disease in man was prompted by Kidd^{1,2}, who observed striking regressions after the injection of normal guinea-pig serum in mice and rats bearing certain transplanted lymphomas. Sera of other species, such as the horse, rabbit and human, were not effective. This information emerged from experiments in which guinea-pig serum was used as a source of complement. Although this serum enhanced the activity of antibody, there was strong tumour inhibition when it alone was used. The cytotoxic effect of guinea-pig serum *in vitro* against tumour cells must have been observed on several occasions by tumour immunologists during experiments with cytotoxic antibody, but the significance of the finding was not appreciated.

Broome³⁻⁵ provided good evidence that L-asparaginase was responsible for the antilymphoma effects of guinea-pig serum after he had found an early paper by Clementi⁶, who investigated the distribution of amino-acid degrading enzymes in the tissues of different animal species. Clementi observed that L-asparaginase was present in the liver and kidney of many species, but in the blood of only one of the animals that he studied—the guinea-pig. Sera lacking L-asparaginase have no

antilymphoma properties. The tumour inhibitory agent and L-asparaginase seemed to be identical in several physical and chemical properties examined. The stability of the enzyme to changes of temperature and pH was found to parallel closely that of the antilymphoma agent. When guinea-pig serum proteins were separated by salt precipitation electrophoresis and chromatography on DEAE cellulose, antilymphoma activity was found only in fractions which contained L-asparaginase. Tumour cells can be selected for resistance to L-asparaginase *in vitro*, and these cells are also insensitive to the enzyme *in vivo* when transplanted to susceptible mice. Purification of L-asparaginase from other sources has shown the powerful tumour inhibitory effect of this enzyme. This finally established the role of L-asparaginase as a tumour inhibitory agent.

Source

L-Asparaginase has been found in the serum of guinea-pigs and related South American rodents^{7,8}, in New World monkeys, in chicken liver⁹ and in some microorganisms such as *Escherichia coli* and *Erwinia carotovora*. The enzymes prepared from different sources do not all have the same properties and some are without effect on tumour growth. Mashburn and Wriston¹⁰ obtained a potent preparation of asparaginase from *E. coli*. Such preparations have been shown to consist of two enzymes, only one of which is active against sensitive leukaemias¹¹⁻¹³. One enzyme of low avidity has no tumour inhibitory action; the other is of high avidity and is a potent antitumour agent. The rate of clearance of the enzyme from the blood may be another factor determining its antitumour effect. The inactive enzyme has an extremely rapid clearance rate from serum. The inactivity of yeast asparaginase can be explained on this basis¹⁴. Whereas a considerable amount of guinea-pig serum

asparaginase remains in the blood for three or more days after a single intravenous injection, yeast asparaginase is almost completely cleared in less than one hour. No inhibition of tumour growth has been found after the administration of yeast asparaginase. The half life of *E. coli* asparaginase in the plasma varies from 8 to 24 h depending on the preparation. Of the two commercial preparations in common use derived from *E. coli*, the Merck preparation has twice the half life in the human circulation of the Bayer preparation¹⁵. Another contributory factor influencing *in vivo* effect may be low activity at physiological pH. Clearly it is very important to include a statement regarding the source of L-asparaginase when describing experiments assessing its biological effect.

Therapeutic Range in Experimental Animals

Tumours vary widely in their sensitivity to L-asparaginase. Complete eradication is possible for some animal tumours whereas the enzyme has no apparent effect on many others. A wide variety of tumours, both spontaneous and induced, in different animal species have been shown to regress, often completely, when treated with L-asparaginase. The implanted leukaemia known as 6C3HED in mice, for example, can be cured by a single dose of L-asparaginase. Boyse *et al.*¹⁶, in a study of 109 recently derived leukaemias of the mouse, showed that sensitivity to suppression by guinea-pig serum is a common property of transplanted leukaemias of certain classes. The sensitive leukaemias included five that arose spontaneously in mice of strains with a low incidence of leukaemia and twenty-one that were induced by X-radiation. Most of the tumours in animals which are susceptible *in vivo* have been derived from the reticulo-endothelial system. The tumour inhibitory activity is not restricted to mouse leukaemias but has been found to occur with transplanted rat tumours^{1,17,18} including a carcinosarcoma¹⁹, and with primary dog lymphosarcomas²⁰.

Chemistry and Mode of Action

The molecular weight of L-asparaginase is approximately 140,000 and only small quantities reach the extravascular compartment. Very small quantities are found in urine, cerebrospinal fluid, tissues or red blood cells³⁹. The enzyme is stable and solutions retain their activity for many weeks. The enzyme is unique among chemotherapeutic agents used in the treatment of neoplastic disease in man, for its action is based on a metabolic defect of certain cancer cells. Unlike normal cells these malignant cells can only synthesize asparagine slowly and are dependent on an exogenous supply. The action of L-asparaginase is to destroy asparagine, resulting in the death of cells which are asparagine-dependent. Asparagine is present in most, if not all, animal proteins. Cells which are incapable of synthesizing asparagine in sufficient quantity from other sources cannot synthesize protein in the absence of an exogenous supply of asparagine^{5,21,22}. Protein synthesis is one of the early biochemical events inhibited after the application of L-asparaginase to sensitive cells.

In some experimental animal work, the presence of asparagine synthetase has been correlated with a cell's resistance to the action of L-asparaginase²³⁻²⁸. For example, 6C3HED cells grown *in vitro* have been shown to synthesize asparagine at a high rate, and they are resistant to the action of L-asparaginase which deprives the cells of an exogenous supply. The high rate of asparagine formation is associated with the presence of asparagine synthetase, which is involved in the synthesis of asparagine from glutamine and aspartate. 6C3HED cells selected for resistance to L-asparaginase *in vitro* can be transplanted into mice, and the leukaemia thus produced is resistant to the *in vivo* action of L-asparaginase. Further investigation on the content of asparagine synthetase in different animal tumours has revealed a reasonably good correlation between the presence of this enzyme and resistance to the *in vivo* action of L-asparaginase. The L-asparaginase-resistant form of the Jensen sarcoma has a greater capacity for aspara-

gine synthesis than either a susceptible line or normal liver²³. Lymphomas which are resistant to L-asparaginase contain more asparagine synthetase than either susceptible tumours or normal tissue²⁶. Resistant tumours respond to L-asparaginase with large increases in their content of asparagine synthetase, a moderate response occurs in normal tissues and susceptible tumours give only a transient response.

In vitro Testing of Malignant Cells

In vitro tests have been shown to be unreliable in predicting the clinical response to treatment with L-asparaginase in man. This is hardly surprising—the tests pay no attention to the agent's absorption, detoxication, excretion, distribution and duration in the body. The mechanisms whereby cells can repair or circumvent damage by the agent may be very different *in vivo*. Two tests have been used. One test measures asparagine dependence by assessing the *in vitro* incorporation of ¹⁴C-l-valine or ³H-uridine by tumour cells in the presence or absence of asparagine. Some people have suggested that this test can provide useful predictive information²⁹⁻³². With this technique it is possible clearly to distinguish between animal tumours which are sensitive and resistant to L-asparaginase. In man, however, results have not been so clearcut. Tests indicating asparagine dependence of acute lymphoblastic leukaemia cells have shown a positive correlation between dependence *in vitro* and response of the disease to treatment with L-asparaginase. Unfortunately, the test is not reliable in predicting response and several patients with little asparagine dependence *in vitro* have achieved a complete remission when treated with L-asparaginase. It is unsafe to rely on this test in deciding whether to treat with this enzyme or not. The test is even more unreliable if other tumours are considered. Malignant melanoma cells are frequently inhibited by L-asparaginase in tissue culture but treatment with the enzyme *in vivo* is ineffective.

Another *in vitro* test is the assay of asparagine synthetase activity in malignant tissue. Early work in man has not been easy because of the difficulty of assaying asparagine synthetase and because other enzymes may well be concerned in the synthesis of asparagine. Normal cells which are relatively resistant to L-asparaginase, and might be expected to contain large amounts of asparagine synthetase, contain small amounts of this enzyme.

Haskell *et al.*³¹ showed that there was almost always very little asparagine synthetase in human malignant tissue before treatment. Assays of the pretreatment concentrations of this enzyme were not useful in predicting response to L-asparaginase. In contrast, among patients whose asparagine synthetase activity was assayed during and after treatment, there was a marked difference between resistant and sensitive groups. In all patients giving a good response to L-asparaginase, the subsequent concentration of asparagine synthetase was within one standard deviation of the pretreatment value for that group, whereas the patients failing to respond to therapy all had elevated greater concentrations of asparagine synthetase. This suggests that the appearance of asparagine synthetase during or after therapy plays a role in human tumour resistance to L-asparaginase, as has been shown in murine tumours.

Normal cells are affected by L-asparaginase but tend to be less sensitive to the effects of asparagine deprivation than sensitive tumour cells. L-Asparaginase given at the time of partial hepatectomy blocks the wave of mitosis which usually occurs 24 to 35 h later. In contrast to tumour cells, the liver seems to be able to overcome the inhibition, and after 48 h mitosis is even more intense than in normal animals³³. The enzyme can also markedly inhibit the transformation of normal human lymphocytes which takes place *in vitro* in response to stimulation with phytohaemagglutinin, allogeneic cells or antigens to which the cells have previously been sensitized³⁴. As might be expected from this, L-asparaginase is an immunosuppressive agent and has been used in the treatment of

diseases in which immune reactions play a part in pathogenesis³⁵. The enzyme has also been shown to be embryotoxic³⁶.

Therapy in Man

L-Asparaginase is of value in the treatment of three diseases; acute lymphoblastic leukaemia (ALL), leukaemic lymphosarcoma and lymphosarcoma. Useful regressions and remissions have been obtained in these diseases using the enzyme as a single agent. Patients with acute lymphoblastic leukaemia respond better than those with diseases in which there are masses of tumour tissue as in lymphosarcoma, but remarkable regressions of large lymphosarcomatous masses have occurred.

Dolowy *et al.*³⁷ were the first to treat a patient suffering from ALL with L-asparaginase. Although the number of blast cells in the peripheral blood decreased, the patient, an eight year old boy, died within ten days. Hill *et al.*³⁸ were the first to obtain a complete remission in ALL, and since then the use of L-asparaginase in the treatment of ALL has become widespread.

More than half of the patients with ALL treated in the early stages of the disease achieved complete remissions. About one-third achieved remissions if the enzyme was used late in the course of the disease. The largest number of patients was treated in the Memorial Hospital, New York³⁹. Of seventy-three patients with ALL treated with L-asparaginase for more than 14 days, 62% achieved a complete remission with a median duration of 60 days. In those remitting who had meningeal features, there was a reduction in cell and protein content of the cerebrospinal fluid (CSF). This was rather surprising in view of the poor entry of the enzyme into extravascular tissues. The molecular weight of the enzyme is approximately 140,000 and only small quantities reach the urine and CSF. In spite of this, there is little asparagine in CSF during treatment and this may well be the explanation of the partial success. Meningeal leukaemia has been treated by direct instillation of L-asparaginase into the CSF, but with attendant troublesome side-effects. The remissions obtained in this disease were no longer than those obtained by more conventional treatment.

Continuing maintenance with L-asparaginase has not prolonged remission in patients with ALL⁴⁰. Nearly all patients relapsing during treatment are resistant to further treatment with L-asparaginase. Occasionally, second remissions have been obtained in patients who were not maintained on the enzyme.

One of the most interesting features of the action of L-asparaginase is the tremendously high therapeutic index when it is used in the treatment of ALL. Remission rates with different doses of the enzyme are shown in Table 1. The therapeutic index in this situation is greater than 500, which is considerably better than for any other antitumour drug. This is true even when sensitive experimental animal tumours are considered. The highest therapeutic index so far recorded using drugs other than L-asparaginase is for the use of 'Melfalan' in the treatment of the animal tumour PC6 (a plasma cell tumour). A therapeutic index of 280 was achieved in this system (personal communication from T. A. Connors). All other drugs used in the treatment of acute leukaemia in man are usually given in doses close to the toxic range. All therapeutic indices are low and are invariably less than ten.

Table 1 Remission Rates in Acute Lymphoblastic Leukaemia using Different Doses of L-Asparaginase (ref. 40)

Dose of L-asparaginase IU/kg/day	No. of patients	No. of complete and partial remissions
10	12	6
200	10	6
1,000	22	14
5,000	11	7

Unfortunately, L-asparaginase has a very limited place in the treatment of human neoplastic diseases. The enzyme is only of value in the treatment of ALL and lymphosarcoma and has not yet been shown to be of value in other forms of leukaemia or solid tumours. Even in those diseases where remissions are obtained these are invariably of short duration. The promise which L-asparaginase held when first introduced has not been realized. This may be due to difficulty of access of the enzyme to tissue spaces or resistance of the malignant cells to its action.

Leukaemia and Combination Studies

Although L-asparaginase is of no proven value in the treatment of acute myelogenous leukaemia (AML), a precipitous decrease in the peripheral blood blast count is usually observed within the first few days of treatment. Occasionally, patients with this disease achieve a complete remission but this is infrequent. About 10% of patients have a complete remission when receiving this treatment⁴¹. Using high dose regimes, Hill *et al.*³⁵ obtained complete remissions in 18% of patients with AML. This remission rate is lower than in an earlier report which included patients of a lower mean age⁴².

Trials using L-asparaginase in combination with cytotoxic drugs are under way in an attempt to increase remission rates in AML. Such studies were prompted by finding synergism between L-asparaginase and certain cytotoxic drugs when used against leukaemia in mice⁴³. In mouse leukaemia L5178Y, many different agents such as vincristine, various purine antagonists, actinomycin D, daunorubicin, adriamycin and cytosine arabinoside potentiate the antileukaemic effect of L-asparaginase. Most drugs are more effective when given before L-asparaginase. The potentiating effect in mouse leukaemia may be due to the inhibition of normal cells which may be synthesizing asparagine and supplying it to the asparagine-dependent leukaemic cells. Some combinations may be antagonistic and cells in culture deprived of asparagine are resistant to the action of methotrexate⁴⁴. The time and order in which the drugs are given may be of immense importance.

The few trials which have been done with human subjects do not reveal any great benefit from the addition of L-asparaginase to a therapeutic regime of cytotoxic drugs. Indeed, some patients have made less progress with L-asparaginase in combination and the enzyme may have increased the side effects of the other agents. This effect may well be due to the known toxic effect of L-asparaginase on the liver. This phenomenon has been observed in two trials, one concerning AML in adults and the other concerning ALL in childhood^{42,45}.

A group of workers in the United States, known as the Acute Leukaemia Group B, has presented data indicating that using L-asparaginase in combination with prednisone, vincristine and daunorubicin is superior to L-asparaginase alone in inducing remissions in children with previously treated ALL in relapse. In addition, there seemed to be some advantage in using high dose weekly L-asparaginase rather than daily administration although the difference between the two groups was rather small (Table 2).

Toxicity in Man

Treatment with L-asparaginase is nearly always accompanied by troublesome side effects. Fortunately, serious toxicity is uncommon⁴⁷⁻⁴⁹. Therapy is usually attended by nausea, vomiting and anorexia with weight loss. Fever was common with earlier preparations but recent preparations are non-pyrogenic or cause very little fever. The enzyme is a foreign protein and allergic reactions occur in about one-fifth of people treated. These reactions may occur after the first dose but more usually during the second week of therapy. Anaphylaxis with hypotension, sweating and bronchospasm may occur or perhaps urticaria. If allergic reactions develop

Table 2 Comparison between Remission Rates in Acute Lymphoblastic Leukaemia (ALL) using L-Asparaginase Alone or in Combination with Prednisone, Vincristine and Daunorubicin

Complete remission rates in ALL		
Daily L-asparaginase × 15	33 %	21/51 (41 %)
Weekly L-asparaginase	46 %	
Daily L-asparaginase + Pred VCR DR	63 %	30/44 (68 %)
Weekly L-asparaginase + Pred VCR DR	75 %	

Pred, prednisone; VCR, vincristine; DR, daunorubicin.
These data were obtained by the Acute Leukaemia Group B.

during treatment with L-asparaginase obtained from *E. coli*, treatment may be changed to the enzyme from *Erwinia carotovora*, which has no cross reactivity. Desensitization is possible but potentially dangerous. Skin testing before administration is probably a wise precaution.

Although L-asparaginase is not associated with the myelotoxic effects associated with most antitumour agents, it has a wide range of toxic effects on other organs, including the liver, pancreas, kidneys, blood clotting systems and brain. The part played by contaminating glutaminase or endotoxin in these side effects is unknown. There may be toxic hepatitis with fatty change associated with higher than normal concentrations of liver enzymes in the serum, and jaundice may occur. Hypoalbuminaemia with oedema is a common feature if treatment is prolonged beyond two weeks. These changes are usually reversible. A depression of serum cholesterol is related to a depression of lipoprotein synthesis by the liver. Coagulation abnormalities occur with prolongation of the prothrombin time or partial thromboplastin time, but serious haemorrhage is rarely observed. The disorders are chiefly due to reduced synthesis of coagulation factors, but intravascular coagulation with a consumption coagulopathy has been observed. Occasionally there is an increase in blood urea. Central nervous system abnormalities with depression associated with personality disturbances and acute organic brain syndromes can also occur. The mental confusion seems to be related to age and dose. Pancreatitis has occurred in a few cases. Hyperglycaemia may be a problem; the cause is uncertain but pancreatic dysfunction may sometimes be involved. In some individuals with hyperglycaemia, the serum insulin has been normal as measured by radioimmunoassay and the presence of a faulty insulin molecule has been postulated. The hyperglycaemia is reversible and controllable with insulin. Another side effect is immunosuppression involving both cell-mediated and humoral immunity⁵⁰.

Fortunately, in spite of the long list of possible complications, serious side effects are not common. Certainly they are much less troublesome than many which accompany the use of cytotoxic drugs. The side effects are usually reversible and dose dependent. The incidence depends to some extent on the type of L-asparaginase used, but the possible complications are similar. The treatment differs from most conventional antitumour treatment because the enzyme is not myelotoxic.

The use of L-asparaginase has provided a new approach in the treatment of human cancer. It is possible that other factors will be found which are more essential for tumour cell growth than for normal cells. In this article I have indicated the useful role of this therapy in the treatment of ALL and lymphosarcoma. The future may well hold a more important role for this type of antitumour agent, possibly in combination with more conventional treatment.

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Ecology of the Brontosaurs

by

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A reconsideration of brontosaur remains suggests that the largest dinosaurs were not semi aquatic but terrestrial, in spite of their high external nares.

THE order Sauropoda includes the largest dinosaurs and the greatest land animals of any age. Well known sauropods, such as *Apatosaurus* (= *Brontosaurus*), *Brachiosaurus*, *Diplodocus* and *Cetiosaurus*, reached lengths approaching one hundred feet and weighed in life probably upwards of 20 or 30 tons. Almost invariably the sauropods, or brontosaurs, are restored as swamp and lake-dwelling herbivores¹. A re-examination of brontosaur anatomy, however, shows that the evidence for these supposed semiaquatic habits is weak.

The feature most often cited in favour of semiaquatic habits for sauropods is the position of the external nares^{1,2}. The external bony narial orifice in sauropods is usually very large and extends posteriorly to just in front of the orbit. In a great many aquatic and marine reptiles, past and present, ichthyosaurs, plesiosaurs, placodonts, nothosaurs, mosasaurs, pleurosaurs and champsosaurs, the external nares are just in front of the eyes. But in these water-living reptiles the external nares are very small openings, often low on the side of the face; in contrast, the nares of brontosaurs are usually very spacious and are situated high on the skull. Supposedly the elevated narial position made it possible for these dinosaurs to breathe with the body entirely submerged and only the tip of the nostrils exposed¹. Though such a function may seem to be valuable to an aquatic reptile, the living tetrapods with a narial structure most closely resembling that of brontosaurs are terrestrial animals. In some fully terrestrial lizards, the ground iguanas (*Cyclura*) and desert monitors (*Varanus griseus*), the external nares are high on the snout, very large and extend posteriorly to just in front of the eyes. In these lizards the external naris is filled with a spacious nasal capsule enclosing channels with increased surface area for olfaction and for humidifying and filtering inspired air³. In aquatic reptiles olefaction usually is reduced in importance, and the external nares are usually quite small. Most probably brontosaurs had an enlarged nasal capsule and increased capacity for olfaction and for treating inspired air. In some mammals, tapirs, elephants, the extinct astrapotheres, pyrotheres, and litopterns, the external nares are posterior and large. In these mammals the narial position is associated with a proboscis and not with aquatic habits.

In truly aquatic reptiles, crocodilians, phytosaurs and champsosaurs, the tail is a powerful propulsive organ. In such swimming tails the neural spines are very tall for most of the caudal length. No known brontosaur has this type of tail. In sauropods the height of the neural spines decreases rapidly posteriorly, and the end of the tail is often a slender whiplash like that of many terrestrial lizards.

Sauropod teeth have been described as weak and adapted for pulling up soft water plants¹. Molariform teeth with complex grinding or cutting action are unknown in brontosaurs. Severe tooth-to-tooth and tooth-to-food wear, however, is known from some brontosaurs (*Pelorosaurus*⁴, *Camarasaurus*⁵), and suggests that they fed on coarse vegetation, not water plants.

Brontosaurs may not have needed molariform teeth for grinding tough food; they may have had a powerful gastric mill like that of crocodilians. Recent X-ray motion pictures taken at Yale University have shown ingested mice being ripped and crushed by the stones embedded in the muscular stomach wall of an alligatorine (*Caiman schlerops*). Although the authenticity of isolated finds of dinosaur "gizzard stones" is always suspect, several dinosaur skeletons, including one sauropod⁶, have been found with concentrated masses of small stones among the ribs, and these finds could well represent gastric mills.

A peculiar body configuration—long, broad thorax, short legs (Figs. 1A and B)—characterizes most modern freshwater tetrapods. Among insectivores the highly aquatic *Potamogale* has this long, round-bodied, short-legged, otter-like build. *Hippopotamus* and the short-legged, semiaquatic Brazilian bush dog (*Speothos*) provide further examples of this configuration. In contrast, elephants have very deep thoraces. Brontosaur rib cages were very deep, elephant-like, and not at all like those of hippos (Fig. 1A).

The brontosaur vertebral column has several features associated with the support of the body on dry ground. The trunk vertebrae were stout and short, with tall neural spines bearing massive rugosities where thick interspinous ligaments attached. Extra articulations (hyposphene-hypantra) were developed as well as zygapophyses. Similar development of extra articulations, tall spines, powerful interspinous ligaments, can be seen in large ground-living birds (ostrich, cassowary) and large, carnivorous dinosaurs (*Megalosaurus*, *Tyrannosaurus*). Such trunk-strengthening adaptations are not well developed in hippos.

Much important evidence for brontosaur habits is found in their limb construction. In most mammals the elbow and knee are strongly flexed. This flexure is associated with a galloping gait at high speeds⁷. Very heavy mammals that retain galloping abilities, such as the white rhinoceros, have strong elbow and knee flexure. Although they reach weights even greater than that of white rhinos, hippos have rhino-like elbow and knee flexure (Fig. 1C). Hippos have smaller, less robust limbs relative to their body weight than rhinos. Relatively small, weak limbs are sufficient for hippo locomotory needs because the animal is frequently supported by water and does not have to move over dry land as extensively as rhinos and elephants to forage and migrate. In contrast to hippos and rhinos, elephant limbs are quite straight at knee and elbow. Elephants cannot gallop, and their fastest gait is the amble. The straighter, more columnar limbs of elephants enable the body weight to be carried more directly by the pillar-like limb bones with a minimum of muscular bracing. Straight, elephantine limbs developed in other large terrestrial mammals—uintatheres, pyrotheres and arsinotheres. In most dinosaurs, including the prosauropods that were close to brontosaur ancestry, elbow and knee were strongly flexed. In brontosaurs, however, the amount of knee and elbow flexure was greatly reduced (Fig. 1C). Brontosaur limbs were very straight, columnar, and elephantine. The combination of elephant-like limbs and powerfully braced backbone argues strongly for terrestrial habits for brontosaurs.

Hippos face the problem of traction in soft, yielding substrates around and in lakes and rivers. The digits of hippos are longer and more spreading than those of rhinos and elephants (Fig. 1D). The sitatunga, a marsh-dwelling antelope, shows a similar adaptation in its spreading, elongate, banana-shaped

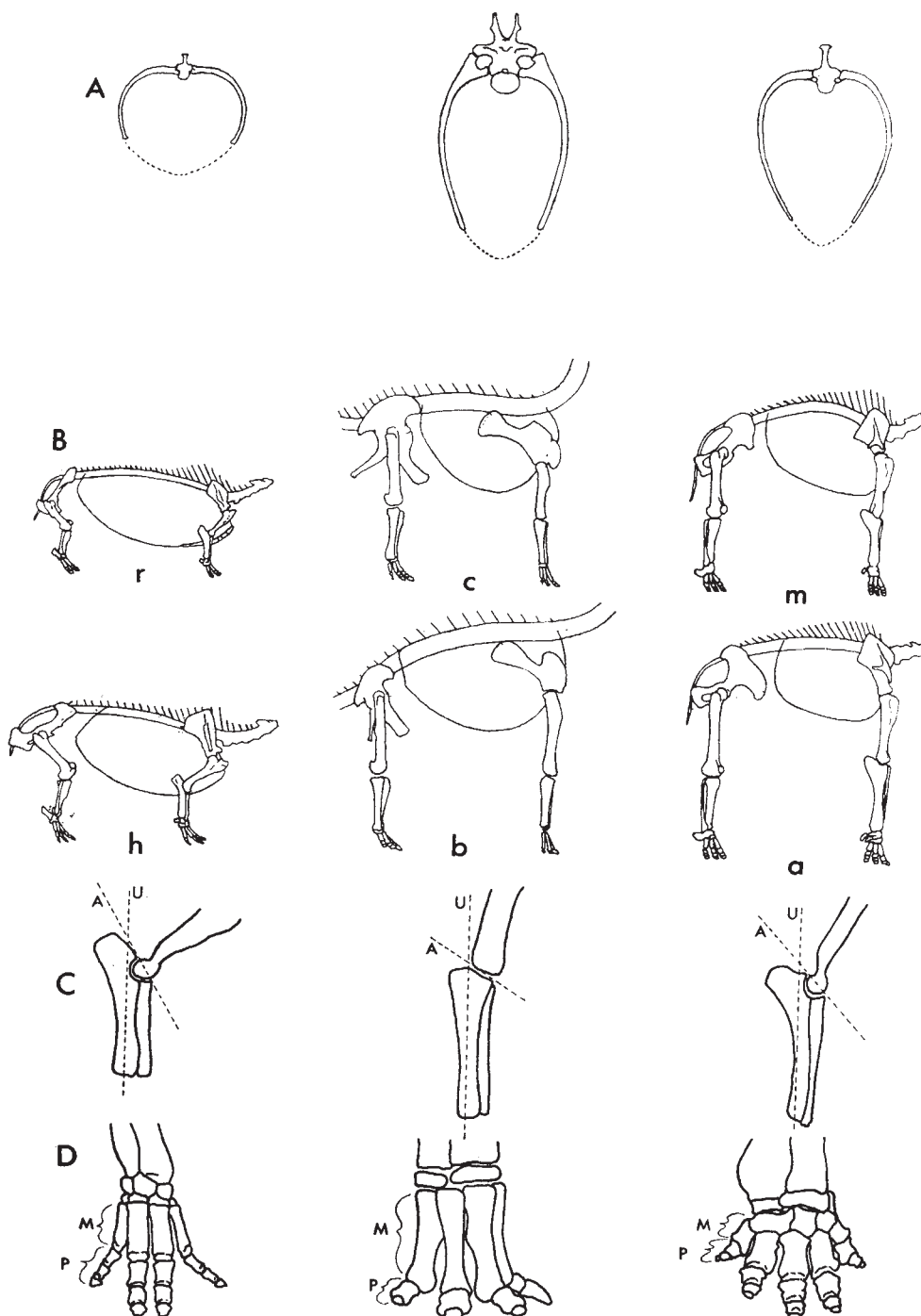
hoofs. Large, presumably fully terrestrial dinosaurs—horned dinosaurs, stegosaurs and ankylosaurs—had moderately long digits of approximately rhino-like proportions. Elephants have very short digits buried within a cushioning pad. Brontosaurus toes were exceptionally short with very abbreviated phalanges (Fig. 1D). Brontosaurus footprints show that the toes were encased in an elephant-like pad⁸. It is difficult to imagine how sauropods could travel over marshy terrain with such compact feet. Elephants are usually quite careful around soft ground, for individuals may become hopelessly bogged down and starve to death⁹.

Most brontosaurus had very long necks which enabled some genera (*Barosaurus*, *Brachiosaurus*) to raise their heads to a 40-foot level. Brontosaurus limbs were usually rather long and elephant-like in proportion. The combination of long limbs and long neck is usually associated with browsing high in shrubs and trees. Elephants have the equivalent of a long neck in their proboscis. Giraffes, okapis, camels and some

antelope (the gerenuk) are long necked high browsers. The largest land mammal of any time was the long legged, rather long necked rhino, *Baluchitherium*. A long reach gives a high browser a greater vertical choice of food than that available to a shorter herbivore. Perhaps it is significant that the largest land mammals, elephants and baluchitheres, were tall creatures with great vertical reach, and that the largest dinosaurs were the tall, long necked sauropods. Hippos have very short legs and necks. The hippo-like rhinos of the Eocene and Oligocene (amynodonts) and Miocene and Pliocene (*Teleoceras*) also had small limbs and short necks (Fig. 1B).

The diversity of sauropods also argues for terrestrial habits. Freshwater lakes and rivers offer less opportunity for adaptive radiation of herbivorous tetrapods than terrestrial habitats. Hippo-like herbivores have never numbered more than one or two sympatric species at any one point in time. A few species of hippos lived in the Pleistocene; a few teleocerine rhinos in the Pliocene; a few amynodont rhinos in the Oligocene–Eocene.

Fig. 1 Comparison of hippo (left), brontosaurus (centre), and elephant (right). **A**, Cross section of thorax of hippo (*Hippopotamus*), brontosaurus (*Diplodocus*), and elephant (*Loxodonta*). **B**, Outlines of right side of skeletons drawn to same acetabulum-to-shoulder length. r, Hippo-like rhino (*Teleoceras*); h, hippo (*Hippopotamus*); c, brontosaurus (*Camarasaurus*); b, brontosaurus (*Brachiosaurus*); m, elephant (*Mastodon*); a, elephant (*Archidiskodon*). Full length of brontosaurus necks not shown. **C**, Section through elbow to show orientation of articular surfaces. On the left is hippo (*Hippopotamus*); in the centre is brontosaurus (*Camarasaurus*); on the right is elephant (*Elephas*). **A**, axis of elbow facets on humerus; **U**, axis of facets on the radius and ulna. **D**, Right fore feet of hippo (*Hippopotamus*); brontosaurus (*Diplodocus*); elephant (*Mastodon*). **M**, metacarpals; **P**, phalanges.



In contrast, all through the Cainozoic a great variety of land herbivores have coexisted—elephants, mastodons, horses, long-legged rhinos, chalicotheres, camels of several varieties, entelodonts, anthracotheres, cervids, bovids, giraffids, etc. In Late Jurassic deposits sauropods are very diverse. In a single quarry in the Morrison Formation of Wyoming and Montana five genera can be found together—*Apatosaurus*, *Barosaurus*, *Brachiosaurus*, *Camarasaurus* and *Diplodocus*⁴. Considerable variety is present among these genera in details of limbs, neck, trunk and tail. I believe that it is inconceivable that so many genera of sauropods could have evolved in the context of a lake-swamp environment.

The sedimentology of the sauropod-rich Morrison formation offers more refutation of the supposed aquatic habits. Morrison brontosaurus quarries represent flood-plain deposits, not lakes and swamps¹⁰. Moreover, Morrison brontosaurus are usually found with various fully terrestrial dinosaurs (megalosaurus, stegosaurs, camptosaurs). In contrast, fossil hippo-like mammals, such as the amynodont rhinos of the Oligocene, are often dominant in coarse river channel deposits while the contemporaneous terrestrial faunas are more common in fine grained flood-plain siltstones and shales¹¹.

A frequent assumption is that sauropods fled to the water to escape carnivorous theropod dinosaurs¹, but there is no evidence of this. Sauropods, like elephants today, may have been able to swim when necessary. However, the theropods seem better equipped for swimming than their supposed sauropod prey. Theropods such as *Allosaurus* and *Megalosaurus* had long, powerful hind limbs with spreading toes much like those of large ground-living birds. Emus, rheas and cassowaries are good swimmers, propelling themselves by strong kicks¹². Footprints of sauropods indicate that at least some genera travelled in herds⁸. On land a herd of these gigantic dinosaurs would seem well able to defend itself by lashing the long, whip-like tails or threatening to crush attackers underfoot.

Although figures of sauropods shoulder-deep in swamps are abundant in museums and publications, the anatomy of these dinosaurs points to fully terrestrial, elephant-like habits. The high, posterior position of the large external nares is certainly not evidence enough to prove aquatic habits since terrestrial reptiles and mammals share this feature with sauropods. The sauropod back, braced by powerful ligaments, tendons, and extra articulations, and the straight, elephantine limbs are obvious adaptations for supporting great weight for long periods on land. The deep chest, long limbs, and long neck seem to be browsing adaptation and not related to a hippo-like existence.

The impact of brontosaurus on the Mesozoic terrestrial ecology must have been enormous. The herds of different sympatric sauropod species must have opened up thick forest and kept undergrowth from becoming dense, much as elephants do today in Africa. Smaller herbivorous dinosaurs adapted to open woodlands and plains must have depended on sauropods for keeping such habitats from being overrun by thick jungle.

Received October 12, 1970.

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Isolation and Proof of Structure of Wildfire Toxin

by

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For two decades wildfire toxin has attracted attention because of its curious biological and chemical properties. Its structure, reported here for the first time, may be a clue to its mode of action: it is one of the few naturally occurring β -lactams.

WILDFIRE disease of tobacco is perhaps the most thoroughly studied of all toxin-mediated plant diseases. Yet twenty years of work on the chemistry and biochemistry of wildfire toxin did not reveal its structure.

This situation has resulted principally because wildfire toxin has a marked instability and readily isomerizes to a biologically inactive compound. This instability has led to the isolation of impure toxin, which has vitiated the interpretation of much early chemical data. I report here a two-step method of isolating pure wildfire toxin, some chemical properties of the toxin, and a proposed chemical structure (Fig. 1).

History of the Problem

Wildfire is a highly infectious leafspot disease of tobacco plants. The disease, which gained its name from its rapid and destructive spread through tobacco fields, was first reported in 1917 in North Carolina¹ and was soon recognized as the most destructive disease affecting tobacco. Losses were frequently severe; occasionally whole fields of tobacco were obliterated². The disease has been brought under control by

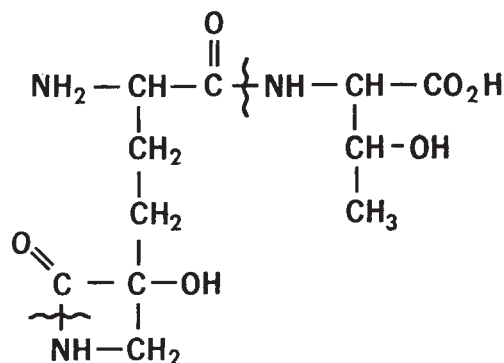


Fig. 1 Structure of wildfire toxin. Hydrolysis of the toxin cleaves the bonds marked by wavy lines and gives the two amino-acids threonine (on the right) and tabtoxinine (on the left).

empirical measures, and is no longer of economic importance, but scientific interest has continued and increased.

In plants affected by wildfire disease, the leaves are covered with circular yellow lesions about 1 cm across. From the centre of these chlorotic lesions, *Pseudomonas tabaci*, the bacterium responsible for the infection, can be isolated and cultured *in vitro*. Cell-free culture filtrates can be used to reproduce the signs of the disease: inoculation of the leaves of healthy tobacco plants (or almost any other plant species) with the filtrate produces the circular yellow lesions characteristic of wildfire³ (Fig. 2). This suggests that the conspicuous signs of wildfire are caused by an exotoxin.

Systematic work on wildfire toxin began in the early 1950s when a team headed by Woolley and Braun developed a method of assaying and concentrating the toxin⁴. These investigations, although hampered by the instability of the toxin, have provided a foundation for all subsequent work in this field.

On the basis of the chemical reactions of their purified toxin, Woolley *et al.* suggested α -lactylamino- β -hydroxy- ϵ -aminopimelic acid lactone as the structure of wildfire toxin (Fig. 3)⁵. Subsequent work⁶⁻⁸ disproved the proposed structure; nevertheless, this structure gained wide acceptance and is quoted in recent literature.

In the past decade, work on wildfire toxin has focused on its



Fig. 2 Comparison of the biological effects of wildfire disease with those of wildfire toxin. The chlorotic lesions on the left were produced by infection with *P. tabaci*; those on the right by a solution of pure wildfire toxin. The toxin reproduces the characteristic sign of the disease.

mode of action^{9,10}. It is highly toxic to a wide variety of organisms: bacteria, algae, higher plants and mammals^{11,12}; 0.05 μg produces a 2 mm lesion on a tobacco leaf. Its toxic effects are completely reversed in many organisms by glutamine and also, in some organisms, by methionine¹³. It has many similarities in its mode of action to methionine sulfoximine, a well studied metabolic inhibitor. There is, for example, preliminary evidence that wildfire toxin, like methionine sulfoximine, is a potent inhibitor of the enzyme glutamine synthetase^{14,15}. The continued interest in the mechanism of action of wildfire toxin¹⁶ clearly calls for an unequivocal determination of its structure.

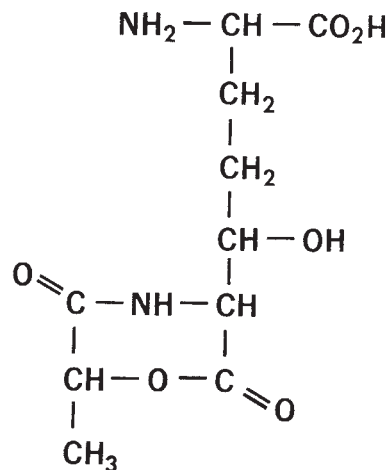


Fig. 3 Structure for wildfire toxin proposed by Woolley and his co-workers.

Isolation of Wildfire Toxin

Pseudomonas tabaci (isolate Pt3, from the International Collection of Phytopathogenic Bacteria, Davis, California) was grown in 15 l. batches in Woolley's medium at 25° C with stirring and vigorous aeration⁴. During production and isolation, toxin content was monitored by automatic amino-acid analysis and by leaf bioassay⁸. Cultures were usually collected 3 days after inoculation. For isolation of the toxin, a 30 l. batch of cell-free filtrate was acidified to pH 2.5 and passed over a 4 kg column of 'Dowex AG-50W X2' resin (50-100 mesh), which had been equilibrated with 1 M NaCl adjusted to pH 2.5. The toxin was then eluted with 1 M pyridine; it emerged with the pH change in a volume of about 1 l., which was pooled and lyophilized. This step typically effected a thirty-fold concentration (before lyophilization) and a 200-fold purification. The crude toxin was obtained about 35% pure by weight, and the overall yield was 85 to 95%.

Half of the crude toxin was further purified by chromatography at 4° C on a 7.5 $\times$ 125 cm column of 'Dowex AG-50W X2' (200-400 mesh) with a 0.2 M pyridine-acetate buffer of pH 3.1. More than 99% of the biological activity emerged in a single peak, which was distinctly asymmetrical*. When the first half of this peak was pooled and lyophilized, it yielded about 200 mg of pure wildfire toxin as a fluffy, off-white powder. In repeated attempts I was unable to crystallize the toxin.

Chemistry of the Toxin

Characterization of the wildfire toxin and evidence for its purity were obtained by chromatography, microanalysis,

* Approximately 1 per cent of the biological activity was associated with a different compound, which was not characterized further. The asymmetry of the major peak was due to a congener of wildfire toxin which possessed biological activity and gave serine and tabtoxinine when hydrolysed. These and other facts suggest that this compound is a homologue of wildfire toxin in which the methyl group of wildfire toxin (Fig. 1) is replaced by a single hydrogen. I propose for this compound the designation wildfire toxin S (S for serine).

spectral methods, and by degradation to more stable compounds. Thus ion exchange chromatography of the toxin on an automatic amino-acid analyser according to the method of Spackman, Stein and Moore¹⁷ gave a single symmetrical peak in the position normally occupied by alanine; a trace component (less than 10%) was also detected. This trace impurity was subsequently shown to be a breakdown product of the toxin, and its characterization is described later. Wildfire toxin gave a single spot on thin-layer chromatography in three different solvent systems. Electrophoresis demonstrated that the toxin migrated as a neutral species at pH 5.0. Microanalysis of a sample dried *in vacuo* for 3 h at 100° C gave values corresponding to $C_{11}H_{19}N_3O_6$: found, C, 45.30; H, 6.78; N, 14.19; ash, 0.3%; loss on drying, 4.2%; $C_{11}H_{19}N_3O_6$ requires C, 45.67; H, 6.62; N, 14.53. Solutions of the toxin showed no absorption in the visible range and only end absorption in the ultraviolet. Infrared spectroscopy of the toxin in KBr had a broad band at 3,400–3,250 cm^{-1} ; three resolved carbonyl bands at 1,740, 1,670 and 1,600 cm^{-1} ; and bands at 1,380, 1,205, 1,075, 1,000, 975 and 940 cm^{-1} .

A striking and informative nuclear magnetic resonance (NMR) spectrum of wildfire toxin was obtained in acid conditions at 220 MHz; Fig. 4 shows the spectrum and the assignment of each signal. The location of titratable groups in the toxin was determined from the changes which occurred in the spectrum in neutral and basic conditions. The positions of the signals at $\delta=1.23$, $\delta\approx 2.1$, and $\delta\approx 3.4$ were not affected by pH (δ is the chemical shift in p.p.m.); these signals account for nine of the twelve carbon-bound protons. The remainder of the spectrum consisted of a one-proton triplet at $\delta=4.24$ and a two-proton multiplet at $\delta\approx 4.5$; both of these signals

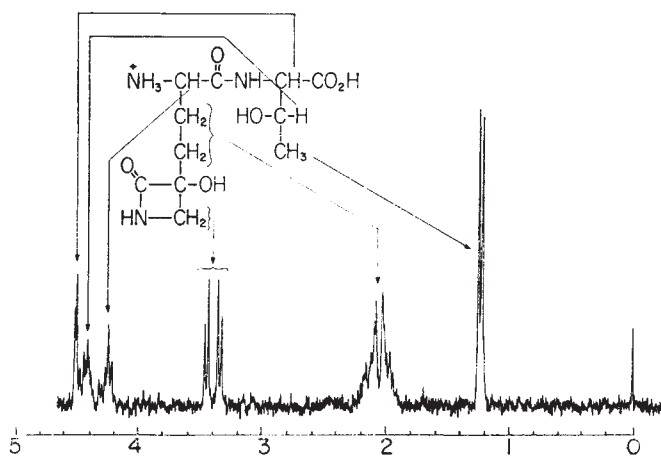


Fig. 4 NMR spectrum of wildfire toxin in D_2O (pH 1.6) at 220 MHz. The scale gives the chemical shift in p.p.m.

were pH-dependent. When their positions in acid and base were compared with their positions at neutrality, a simple pattern was apparent. Basification produced an upfield shift (0.71 p.p.m.) of the one-proton triplet, while acidification left this resonance unchanged (0.01 p.p.m.). Conversely, acidification produced a downfield shift of the two-proton multiplet (0.27 p.p.m.), while its position was almost unchanged on basification (0.04 p.p.m.). These shifts demonstrate that the one-proton triplet is near an ammonium group, and that the two-proton multiplet is near a carboxylate group (compare the arguments of Sheinblatt)¹⁸.

Double resonance experiments further elucidated the environment of the three pH-dependent protons: the one-proton triplet was shown to be coupled to the four methylene protons at $\delta\approx 2.0$ and the two-proton multiplet to the methyl group at $\delta=1.23$. Irradiation of this methyl group collapsed the two-proton multiplet to an AB system with a coupling constant of 4 Hz.

These data are consistent with the structure shown in Fig. 1. This formula is also supported by various degradations of the toxin. Hydrolysis gave the two amino-acids threonine and tabtoxine. These were isolated and identified by chromatography, spectroscopy and by further degradation. The threonine was shown by chromatography and polarimetry to be L_3 -threonine; this is the common isomer found in protein hydrolysates. The infrared spectrum of the isolated material was virtually identical to that of authentic L_3 -threonine.

Tabtoxine is the trivial name proposed by Woolley and his co-workers for the amino-acid which they isolated from toxin hydrolysates¹⁹; the structure they proposed was subsequently withdrawn^{6,7}. A comparison of my material with an authentic sample prepared by Woolley is described later. The mass spectrum of the tabtoxine that I isolated showed a weak peak at $m/e=207$ (presumably the " $M+1$ " ion) and a strong peak at $m/e=170$ (probably formed by the loss of two molecules of water from the parent ion). The accurate mass of the latter peak corresponded to that of $C_7H_{10}N_2O_3$ (found: 170.1681; $C_7H_{10}N_2O_3$ requires 170.1691). Tabtoxine migrated as a neutral molecule at pH 5.0. It was rapidly destroyed by periodate treatment (0.1 M $NaIO_4$ for 15 min at room temperature and pH 4.50) to give a 70% yield of formaldehyde and, on further oxidation and hydrolysis, a 25% yield of glutamic acid. The toxin itself is stable to periodate (less than 5% destruction in the same conditions).

Threonine was shown to be "C-terminal" in the toxin by Akabori hydrazinolysis²⁰ (16% yield of threonine) and by Dakin-West degradation²¹ (more than 90% destruction of threonine; 67% recovery of partially epimerized tabtoxine).

Inactivation of the Toxin

Structure work on wildfire toxin was constantly impeded by the pronounced instability of the toxin. At room temperature and pH 7 the biological activity of toxin solutions decayed with a half-life of about 1 day; inactivation was much quicker in either acid or base. Chemical examination of solutions of inactivated toxin disclosed the presence of a single major component, which turned out to be an isomer of wildfire toxin. This isomer is biologically inactive (less than 0.1% of the wildfire toxin activity) and cannot be identified with any of the compounds described by Woolley and his co-workers. I propose the trivial name isotabtoxin for this isomer of wildfire toxin. Its isolation and characterization provide another line of evidence for the structure of the parent toxin.

Boiling a solution of wildfire toxin for 60 min at pH 3.0 gave a 95% yield of isotabtoxin, which was isolated by preparative pyridine-acetate chromatography as a fluffy white powder. It appeared homogeneous when subjected to ion exchange chromatography on an automatic amino-acid analyser (emerging midway between valine and cystine) and on thin-layer chromatography in three systems. Isotabtoxin gave somewhat unsatisfactory analytical values, which appeared to be due to its hygroscopic nature. A sample dried 24 h at 100° C gave: C, 44.97; H, 6.65; N, 14.13; ash, 0.3%; loss on drying, 3.4%. $C_{11}H_{19}N_3O_6$ requires: C, 45.67; H, 6.62; N, 14.53. Infrared spectroscopy of a KBr pellet showed a broad absorption at 3,420–3,240 cm^{-1} ; two carbonyl bands at 1,660 and 1,600 cm^{-1} ; and bands at 1,390, 1,310, 1,220, 1,145, 1,078 and 997 cm^{-1} .

The NMR spectra of isotabtoxin were obtained at 220 MHz in acidic, basic and neutral conditions. These spectra closely resembled those of wildfire toxin, with three notable differences: (1) the chemical shift of the α -proton of tabtoxine (see Fig. 5) was independent of pH; (2) the ϵ -protons of tabtoxine were now pH-dependent (basification caused an upfield shift of 0.40 p.p.m.); (3) the coupling constant of the ϵ -protons had increased from about 6 Hz (for wildfire toxin) to about 13 Hz.

These data show that isotabtoxin is formed by an isomerization of wildfire toxin that can easily be rationalized on mechanistic grounds: translactamization of the four-membered

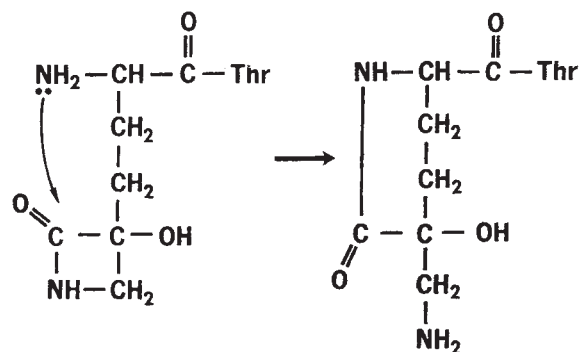


Fig. 5 Isomerization of wildfire toxin to isotabtoxin.

lactam gives the more stable six-membered lactam (Fig. 5). The structure assigned to isotabtoxin is further supported by miscellaneous degradation data. Thus exhaustive dinitrophenylation of isotabtoxin followed by hydrolysis failed to give DNP-threonine; Akabori hydrazinolysis gave a 37% yield of threonine, accompanied by a trace of tabtoxinine. Finally, periodate at pH 4.50 caused a 99% destruction of isotabtoxin in 15 min; further oxidation and hydrolysis of the residue gave a 60% yield of threonine and a 40% yield of glutamic acid.

Summary of Structure Proof

The case for the structure shown in Fig. 1 can be summarized as follows. Hydrolysis of wildfire toxin gives the two amino-acids L_α-threonine and tabtoxinine (Fig. 1). The identity of the threonine is established by comparison with the natural material. The structure of tabtoxinine can be deduced from the following observations. The results of mass spectrometry suggest that the amino-acid is probably C₇H₁₄N₂O₅, but are also consistent with C₇H₁₂N₂O₄ or C₇H₁₀N₂O₃. The electrical neutrality of tabtoxinine and its ready destruction by periodate imply that it is a hydroxydiaminodicarboxylic acid and therefore C₇H₁₄N₂O₅. Oxidation to glutamic acid locates five of the seven carbons; a sixth is detected after periodate oxidation as formaldehyde. These observations eliminate all but a few of the possible structures for tabtoxinine; the choice between the remaining structures can be made quite simply on the basis of the NMR spectrum of the intact toxin.

To find the complete structure of the toxin, two questions must be answered: (1) are there any components of the toxin other than the amino-acids tabtoxinine and threonine, and (2) how are these two amino-acids arranged in the toxin? The NMR spectra of the toxin are useful in excluding the possibility of fragments containing carbon-bound protons: all the observed signals are accounted for by the two amino-acids known to be present. Microanalytical values suggest that the toxin does not contain fragments (such as labile carboxyl groups) which lack carbon-bound protons.

The toxin therefore seems to be an anhydro compound of tabtoxinine and threonine. There are potentially many ways in which these two polyfunctional amino-acids can be combined. The pH dependence of the NMR spectra enormously simplifies the situation by dictating five conclusions: (1) the carboxyl group of threonine is free; (2) the amino group of threonine is bound in an electron-withdrawing linkage; (3) the α-carboxyl group of tabtoxinine (Fig. 5) is blocked; (4) the α-amino group of tabtoxinine, on the other hand, is free; (5) finally, the δ-carboxyl group and the ε-amino group of tabtoxinine are both blocked.

The proof is completed by the following observation: the unusually low coupling constant (6–7 Hz) of the ε-protons of the tabtoxinine moiety is good evidence for the presence of a strained ring^{22,23}, which must necessarily be a β-lactam. This leads directly to formulation of the structure shown in Fig. 1. Data reported in preceding sections but not included in this summary lend further support to this line of reasoning.

Two Different Toxins?

The data and arguments I have presented point convincingly to the formula of Fig. 1 as the correct structure for wildfire toxin. This formula differs markedly from that proposed by Woolley (Fig. 3) which contains lactic acid but no threonine. His formula for tabtoxinine also differs from mine. The magnitude of these discrepancies suggests that Woolley *et al.* isolated a toxin different from that described here.

Several arguments contradict this hypothesis, and although none are conclusive, taken together they form a convincing picture. My toxin was prepared from a strain of *Pseudomonas tabaci* originally isolated by Braun. Within the limits of accuracy of the leaf bioassay, all the biological activity in the culture filtrates could be accounted for by the chemically measured amounts of wildfire toxin. The *R_F* values of wildfire toxin were close to those reported by Woolley. In ascending n-propanol-water (2:1) on Whatman No. 1 filter paper wildfire toxin had an *R_F* of 0.30; Woolley reported an *R_F* of 0.26 for this system. For descending phenol saturated with water I found an *R_F* of 0.50, and Woolley reported an *R_F* of 0.57. Because of the instability of his toxin preparations, Woolley was not able to record any other physical properties which can be used as a basis for comparison, and so recourse to the toxin hydrolysis products must be taken.

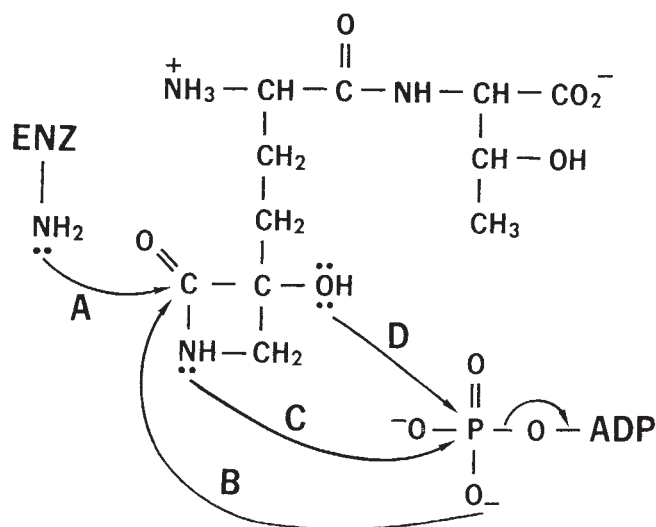


Fig. 6 Speculative mechanisms for the inhibition of glutamine synthetase by wildfire toxin. A shows an attack by the enzyme on the carbonyl of the β-lactam; this would result in acylation of the enzyme. B shows an attack by ATP on the same part of the toxin; this would result in a toxin-ATP anhydride. C and D show an attack by the toxin on the terminal phosphate of the ATP; in both cases a toxin-phosphate would be formed.

An authentic sample of Woolley's tabtoxinine was provided by Mrs D. W. Woolley. I compared this material with tabtoxinine which I had isolated from a hydrolysate of isotabtoxin. The two amino-acids behaved identically on chromatography in several different solvent systems and on reaction with buffered periodate; their infrared spectra were recorded from 2.5 μm to 17 μm and were virtually superposable within the entire range.

I also subjected a toxin hydrolysate, prepared by Woolley 16 yr ago, to chromatography on an automatic amino-acid analyser. The compounds present, identified by their retention times, were found in the following amounts: tabtoxinine, 1.0 mol; threonine, 0.43 mol; alanine, 0.08 mol; and glycine, 0.06 mol. These data suggest that Woolley's toxin was a mixture of various compounds, and that the major component was the toxin which I have characterized. The lactic acid which Woolley demonstrated in his preparations was presumably an impurity. Efficient ion exchange techniques for

handling unstable charged compounds had not been developed, and so it is not surprising that Woolley had difficulty in purifying the toxin.

How Does the Toxin Work?

The structure proof of wildfire toxin presented here will make possible the facile characterization of many related or identical toxins from various pseudomonad species. Their toxin structures may be of value in determining the relation between these species.

The novel structure of wildfire toxin encourages speculation on its mode of action. The β -lactam group has been found in nature only three times: in the penicillin series, in cephalosporin C, and in the pachytermes²⁴. The unusually reactive β -lactam group found in wildfire toxin may well be essential to its toxic effect. Analogy to the proposed mechanisms of penicillin action²⁵ suggests that wildfire toxin exerts its biological effect by inhibiting some enzyme through acylation of the enzyme's active site.

Sinden and Durbin provided evidence that wildfire toxin inhibits the enzyme glutamine synthetase¹⁴. Methionine sulfoximine, biologically similar in most regards to wildfire toxin¹³, is a glutamine synthetase inhibitor that is phosphorylated during its interaction with the enzyme²⁶. This suggests that wildfire toxin is similarly phosphorylated during inhibition (Fig. 6). It should now be possible to investigate this question.

For two decades, work on wildfire toxin has proceeded with impure material of unknown structure. The solution to these problems makes possible a rational attack on the toxin's mode of action.

I thank Dr R. Durbin, Mrs D. W. Woolley, Dr J. M. Stewart, and Dr A. Braun for samples and advice. I also thank many friends and teachers for advice and technical assistance. Part of this work was carried out while I was a graduate fellow at Rockefeller University.

Received November 16, 1970.

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Evidence for a Collapsar in the Binary System ϵ Aur

by

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The mysterious secondary component of ϵ Aur is probably not in a prestellar stage of evolution. It is more likely to be a black hole—a collapsar—formed by a stellar implosion.

EPSILON Aurigae is an eclipsing binary system with a period of 27.1 yr. Its primary star is an F2 supergiant with a mass of the order of 35 Suns. The secondary component is extremely unusual, and the system has long been regarded as very mysterious¹⁻³.

Ordinarily only lines due to the primary are visible in the spectrum of the system. During an eclipse some additional

absorption lines associated with the secondary appear in the spectrum⁴, indicating the presence of small amounts of dilute gas along the line of sight with an excitation temperature similar to that of the primary star. The secondary has a mass of about 23 Suns, however, and it would ordinarily have a luminosity of about 40% of that of the primary². Clearly the secondary is not an ordinary star.

The eclipses are extremely unusual. An entire eclipse lasts just over 700 days, but during the central 330 days a remarkably constant 48% of the primary light is transmitted. The colour of the transmitted light is unchanged, and no polarization effects are produced. Kopal (ref. 2 and unpublished work) has argued convincingly that these effects can only be produced by the obscuration of the primary by a semitransparent disk of particles which are large compared with the wavelength of light. The disk must have approximately constant surface density, except near the outer rim, to produce the flat bottom in the eclipsing light curve. Previous suggestions that the

obscuration might be due to solid particles were made by Ludendorff⁴ and Schoenberg and Jung⁵.

The primary and secondary are separated by some 35 astronomical units. The orbital plane is inclined to the celestial sphere by some 72°. If the occulting disk is oriented perpendicular to the line of sight it would therefore have a radius of some 12 a.u., and considerations of dynamical stability indicate that the radius is unlikely to be much larger than this.

How should this system be interpreted? It is evident that the secondary cannot be a star in any nuclear-burning stage of evolution. Kopal has suggested (unpublished work) that the ϵ Aur system is newly formed, that the primary star has not yet evolved onto the main sequence, and that the secondary is in a prestellar nonluminous stage of evolution in the form of a gaseous and dust-filled disk.

Unfortunately, there are compelling reasons for rejecting this model. A star of 35 solar masses spends very little time in its pre-main sequence contraction; in the vicinity of spectral class F its surface temperature should increase at a rate of 3 to 5 K per yr (ref. 6). This should readily be detectable. I have been investigating the physics of prestellar gaseous disks^{7,8}. If a disk of 23 solar masses is formed with a radius of about 15 a.u., the initial gravitational collapse will heat the central regions to at least 10^4 K, and these regions will radiate with surface temperatures of several thousand degrees. Such an object is entirely excluded by the observations.

Alternatively the primary star could have evolved off the main sequence. In this case it is necessary to assume that the present secondary was originally more massive than the present primary. Thus the present secondary would have evolved off the main sequence somewhat earlier than the present primary. It would have undergone extensive mass loss in the red giant stage, and have come to a catastrophic end-point to its nuclear-burning lifetime.

A remnant mass of 23 Suns is much too large to correspond to a stable white dwarf or neutron star. The alternative is a nonluminous singularity, or black hole. I use the term "collapsar" to refer to that class of black holes formed by stellar implosion.

This form of remnant is entirely in accord with current predictions of supernova hydrodynamic calculations. Wilson⁹ has found that the neutrino-antineutrino transport mechanism for envelope ejection in a supernova event is entirely inadequate to eject mass. Arnett¹⁰ has discussed thermonuclear explosion theories of supernova events, but a star of main sequence mass about 50 Suns will burn carbon and oxygen before forming an electron-degenerate core, so that it cannot be disrupted by a thermonuclear detonation. Thus the bulk of the star which remains at the onset of the implosion is expected to participate in the general relativistic gravitational collapse.

If this picture is correct, the orbit of ϵ Aur gives useful information about the amount of mass ejection that could have accompanied the implosion. If half the mass had been ejected, the remnant would have escaped from the system. If even 10% of the mass were ejected, a quite elliptical orbit would have been produced. Kuiper, Struve and Stromgren¹ determined an orbital eccentricity of 0.33, but a more recent determination by Morris¹¹ gave only 0.17. Because this would not have been an unusual eccentricity for the original system, it seems that not more than a few per cent of the mass could have been ejected at the time of formation of the collapsar.

I shall now consider the origin and nature of the solid particles orbiting in a disk about the collapsar. Mitchell¹² detected excess infrared radiation from ϵ Aur which was quite strong at 9.5 μ m. He showed that this radiation was equivalent to that which would be emitted by a spherical surface of 50 a.u. in radius having a temperature of 500 K.

The F2 primary in ϵ Aur emits about 10^{39} erg/s. Black bodies which absorb unidirectional radiation and reradiate isotropically will therefore have a temperature of 500 K at a distance of 160 a.u. from the primary. The source of the

infrared radiation would therefore seem to be a cloud of solid particles at a distance of 160 a.u. from the centre of mass of the system. Because these particles must approximately maintain this distance, they are probably present in the form of a large disk or ring covering a range of radial distances centred about 160 a.u.

Particles of small size will be ejected from the system by radiation pressure, and particles of somewhat larger size will spiral inward owing to the Poynting-Robertson effect¹³. As is conventional, let us define

$$\alpha = \frac{3L}{16\pi\rho ac^2}$$

where L is the stellar luminosity, ρ is the particle density, a is the radius, and c is the velocity of light. The critical particle size is given by the condition

$$G(M_1 + M_2) = \alpha c$$

where M_1 and M_2 are the masses of the two stellar components of the system. With $L = 10^{39}$ erg/s and $\rho = 3.5$ g/cm³, the critical radius is $a = 0.20$ cm. When both components were on the main sequence, however, the luminosity would have been higher, and particles with radii as large as 0.5 cm were probably blown away from the system.

If all the particles have a radius of 0.5 cm, then the infrared source strength is equivalent to a total mass of 4×10^{30} g of solid material, which would be the chemically condensable component of one solar mass of material.

There has been about 2×10^{14} s during which the Poynting-Robertson effect can have been operating on this material. The time t for an orbit to collapse from an initial radius r is

$$t = \frac{r^2}{4\alpha}$$

The radius from which the present primary could bring in particles of 0.5 cm in 2×10^{14} s is 116 a.u., and this distance would be extended slightly, if allowance is made for the earlier additional contribution of light from the companion star. This result is entirely consistent with the previous conclusion concerning the location of the undisturbed particle reservoir.

As the particles spiral inward they will first come under the local gravitational influence of the collapsar, which lies farther from the centre of mass than the primary. Because the radiation drag experienced by the particles is a dissipative process, they can then be captured by the collapsar. For the particles to be captured dominantly into a plane nearly perpendicular to the line joining the binary components, it is necessary that this line be somewhat tilted relative to the plane of the initial particle orbits. The capture will take place at the time of greatest separation of the components in their orbits.

The captured particles will be maintained at a temperature of about 1,070 K in the radiation flux from the primary. This is sufficiently low so that evaporation of iron and magnesium silicates from the particles is not important.

The particles will spiral into the collapsar due to the continuing radiation drag. For a constant radiation flux incident perpendicular to the direction of particle motion, the particle radius r becomes

$$r = r_0 \exp(-2\alpha t/R^2)$$

where r_0 is the initial particle radius and R is the separation of the binary components. The particle orbits would shrink a factor two in about 8×10^6 yr. Thus there has not been time for any of the particles to have been absorbed by the collapsar.

Although this treatment does not predict a precisely constant surface density of particles in the disk about the collapsar, the departures from constant density are not great over the narrow range of disk radii involved in the eclipse. A more precise treatment is in any case required to determine the surface density near the edge of the disk where the capture takes place.

The model described here seems to account satisfactorily

for the major observational features of the ϵ Aur system. Because of the intrinsically great interest in the possible discovery of a collapsar, it is recommended that much more observational attention be paid to ϵ Aur, particularly in the infrared. Improved orbit determinations are also very desirable, and continued photometric coverage during eclipses.

I thank Professor Z. Kopal for drawing my attention to the peculiarities of ϵ Aur, and for sending me details of his unpublished work. This research was supported in part by the National Aeronautics and Space Administration and the National Science Foundation.

Received October 22, 1970.

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Collapsars, Infrared Disks and Invisible Secondaries of Massive Binary Systems

by

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The supergiant primary of the eclipsing binary system ϵ Aur is probably a star of high mass burning helium in its core. Cameron's suggestion that the invisible secondary is a massive collapsar surrounded by a cool disk of solid particles is thus given further support. A similar object with a disk may be in orbit around the supergiant 89 Her, which has a large infrared excess of unknown origin. The disk could be formed during the initial stage of collapse of the secondary.

INTERPRETATION of the binary system ϵ Aur has always been hampered by observational difficulties. The system consists of a supergiant primary, with a spectrum which is most commonly classified¹ in the range A8 Ia to F2 Ia, and a peculiar invisible secondary. The orbital period is 27 yr, and the primary undergoes eclipses in which the light from the eclipsed star is never completely extinguished. The mass function of the system is $3.1 M_{\odot}$.

Kopal (in unpublished work) has argued convincingly against earlier theories of ϵ Aur and has interpreted the secondary as a large semitransparent disk composed of solid particles, in a prestellar stage of evolution. Thus the primary would of necessity be a massive star in its pre-main-sequence phase of evolution, crossing the H-R diagram as a yellow supergiant. Cameron, in the preceding article, has criticized this interpretation on several counts, although he accepts the existence of the disk of particles. In his view, the primary is an evolved star of high mass, and the secondary, originally the more massive star, has completed its evolution and is at present a collapsar of extremely small radius; the disk (of small mass in

Cameron's theory) has been accreted from the interstellar medium. Previously Trimble and Thorne², in their unsuccessful search among known binaries for a possible collapsed object, mentioned the companion of ϵ Aur as a possible candidate but rejected it on rather superficial grounds.

It has been assumed that the bright luminosity classification of the primary star implies a high mass. That this is not necessarily so can be demonstrated simply from the parameters which specify a stellar atmosphere: namely its chemical composition, effective temperature and surface gravity. Certain models of stars with initially low to moderate mass (refs. 3 and 4 and unpublished work of W. Deinzer) can, in very distended states of advanced evolution after mass loss, attain the specific characteristics of a yellow Ia supergiant. Furthermore, not only is their lifetime in this state comparable with the lifetime of a massive supergiant with the same spectral type, but in general, the birth rate of low-mass stars in space is very much greater than that of massive stars. If ϵ Aur were an evolved system containing two low-mass stars, then the disk around the secondary star could conceivably contain a main-sequence star, or a white dwarf, or even a neutron star. Because the mass of the secondary system is high ($3.6 M_{\odot}$) even in the limit of a very small mass of the primary, the disk would have to be fairly massive if a collapsar or main-sequence star is not embedded inside. Clearly it is important to establish the mass and evolutionary stage of the primary of ϵ Aur in order to interpret the secondary, and this is the object of this article.

The position of ϵ Aur on the sky is not far from that of the association of stars known as Aur OB1. The IAU⁵ boundaries of the association are: $l^{\text{III}} = 168^{\circ}$ to 178° and $b^{\text{II}} = -7^{\circ}$ to $+4^{\circ}$; ϵ Aur is located at $l^{\text{II}} = 163^{\circ}$ and $b^{\text{II}} = +1.2^{\circ}$. Several possible members of Aur OB1 have been listed by Morgan, Whitford, and Code⁶ and by Humphreys⁷. To construct an accurate H-R diagram for the association, the stars listed by these authors and additional stars from Hiltner's⁸ general list of OB stars lying within the formal projected boundaries of the association have been examined for membership on the basis of their radial velocities and apparent magnitudes. Radial velocities were taken from the catalogues of Wilson⁹ and of Petrie and Pearce¹⁰; V and B magnitudes from Blanco, Demers,

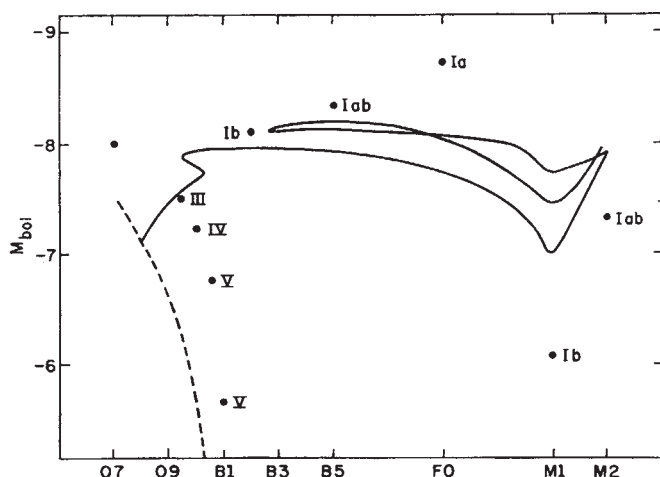


Fig. 1 Bolometric H-R diagram for probable members of the association Aur OB1. Luminosity classes of the stars are indicated (---), unevolved main sequence; (—), evolutionary track of a star of $20 M_{\odot}$. HD 35601 (M1 Ib) may belong to an older population group in Aur OB1, containing also HD 35600 (B9 Ib); this is further suggested by the long evolutionary deviation of the main sequence.

Douglass, and Fitzgerald¹¹; intrinsic B-V colours, bolometric corrections, and effective temperatures from Morton and Adams¹² (for OB stars), Johnson¹³ (for A to K supergiants), and Lee¹⁴ (for M supergiants). A ratio of total-to-selective extinction given by $A_V/E_{B-V} = 3$ has been adopted. The IAU distance to Aur OB1 is 1.34 kpc, which agrees very well with the value derived here from the unreddened apparent magnitudes of the main-sequence stars and Blaauw's¹⁵ calibration of their absolute magnitudes.

Table 1 Probable Members of the Association AUR OB1

Star	Sp	V_{rad} (km/s)	E_{B-V}	M_{bol}
HD 31327	B2 Ib	-5	0.59	-8.1
HD 34656	O7f	0	0.34	-8.0
HD 34921	BO IV: pe	-9	0.44	-7.2
HD 35345	B1 Vpe	+4	0.47	-5.7
HD 35601	M1 Ib	-1.2	0.50	-6.1
HD 35653	B0.5 V	+3	0.40	-6.8
HD 36371	B5 Iab	-0.2	0.42	-8.3
HD 36483	O9.5 III	+6	0.73	-7.5
HD 37536	M2 Iab	+4.8	0.41	-7.3
ϵ Aur	F0 Ia	-2.5	0.35	-8.7

Table 1 lists nine stars which are considered to be association members. Their mean radial velocity is 0 ± 5 km/s, and their mean colour excess is 0.48 ± 0.11 mag., to be compared with -2.5 km/s and 0.35 mag. for ϵ Aur. The mean annual proper motion of the nine stars, the motions of which are listed in the Smithsonian catalogue¹⁶, is $\langle \mu_{\alpha} \rangle = +0.003'' \pm 0.006''$, $\langle \mu_{\delta} \rangle = 0.000'' \pm 0.004''$, where the standard error of the mean motion is here given. With $\mu_{\alpha} = +0.001'' \pm 0.001''$, $\mu_{\delta} = -0.004'' \pm 0.001''$, ϵ Aur could very well be an association member. How much of the measured proper motion is due to orbital motion is not known. Finally, by adopting the distance modulus determined for Aur OB1, an absolute visual magnitude of -8.7 is found for ϵ Aur. This is not incompatible with the value of -8.2 ± 0.6 derived from Strand's¹⁷ combined orbital and astrometric parallax; -7.5 quoted by Morris¹⁸ as having been estimated from the strength of interstellar lines; and -8.5 listed by Blaauw¹⁵ as the average absolute magnitude for an F0 Ia supergiant.

Comparison of polarization measurements of ϵ Aur by Hall¹⁹ with those of OB stars in the general region surrounding ϵ Aur⁸ gives no further information about the distance of the star.

Nor is the spatial arrangement of H I in this general direction usefully determined by 21 cm observations²⁰, because of the lack of distance resolution close to the direction of the galactic anticentre. Although the complex of H II regions in the vicinity²¹ seems to be physically associated with Aur OB1, the complex does not extend as far as ϵ Aur, so that the star is not as clearly affiliated with Aur OB1 as, for example, α Ori is with Ori OB1 (ref. 22). A survey of the list of B stars in Hiltner's⁸ catalogue reveals that no possibility exists of a hitherto unrecognized association around ϵ Aur itself. Certainly the star does not belong to the nearby cluster NGC 1664 ($l'' = 162^\circ$, $b'' = -0.5^\circ$, $r = 0.5$ kpc)²³ because the mean colour excess of the cluster is only 0.16 mag., ϵ Aur lies about 12 cluster radii from the cluster centre, the earliest spectral type of the certain main-sequence members is A0, and the absolute magnitude of ϵ Aur would be only -6.5 if it were a member. It is equally unlikely that ϵ Aur is a runaway star from the much more distant association Aur OB2 ($l'' = 173^\circ$, $b'' = 0^\circ$, $r = 3.6$ kpc). First, the most certain members of Aur OB2 in the IAU list⁵, the O stars, have a very large mean colour excess, 0.60 mag. Second, if ϵ Aur originated at the centre of the association, it would be expected to have a space velocity of at least 200 km/s, and thus an annual proper motion of $\mu = 0.012''$. Third, its absolute magnitude would be unreasonably bright, -10.8 mag., which would require it to have the spectroscopic characteristics of a super-supergiant²⁴, whereas the spectrum seems to resemble basically that of a normal yellow Ia supergiant, particularly in the width of its lines²⁵. It is safe to conclude that ϵ Aur lies at approximately the distance of Aur OB1 and is physically associated with it.

The H-R diagram of the association members is shown in Fig. 1, with the unevolved main sequence²⁶ plotted as a dashed line and the theoretical evolutionary track²⁷ for a star of $20 M_{\odot}$ as a solid line; the uncertain effective temperature of the cool portion of the theoretical track has been adjusted to agree with the observational data for M supergiants.

Apparently, the mass of observed stars that have evolved off the main sequence of Aur OB1 is close to $20 M_{\odot}$. Epsilon Aurigae appears brighter (younger) than the other supergiants if it is an association member. This can be interpreted in several ways, each of which will now be considered in turn.

First, the interstellar extinction for ϵ Aur may not be as large as has been supposed. The intrinsic B-V colour for an F0 supergiant is given by Johnson¹³ as $+0.19$, but two of the values given elsewhere^{28,29} are $+0.24$ and $+0.07 \pm 0.07$. To bring the luminosity of ϵ Aur down to the level of the blue supergiants in Aur OB1 requires an intrinsic B-V colour of about $+0.34$, corresponding, in Johnson's¹³ calibration, to a spectral type of F4. Such a value of intrinsic colour or even a spectral type of F4 is not impossible for ϵ Aur, because of the paucity of suitable standards for Ia supergiants.

Second, because Aur OB1 is a very young association, it is possible that star formation is still going on. The age of the association based on the location of the main-sequence turnup on the H-R diagram is about 7.5×10^6 yr (assuming an initial hydrogen content of 70%), and it is well known that star formation in some young stellar groups can extend over as much as 10^7 yr³⁰. As if in support of this idea, there is the possible presence of an O7f star in Aur OB1 (Fig. 1). Now ϵ Aur lies at least 230 pc from the centre of Aur OB1, and, if it was formed inside the association, it must surely be old compared with the 10^3 - 10^4 yr which represent the pre-main-sequence age of a massive yellow supergiant³¹; otherwise ϵ Aur would have an enormous space velocity. Although massive stars may not always form in associations, the available evidence to the contrary is scarce and not very conclusive³². It is thus reasonable to conclude that ϵ Aur is in a post-main-sequence phase of evolution.

If ϵ Aur has travelled from the centre of Aur OB1 out to a distance of 230 pc during a lifetime of 6.5×10^6 yr (appropriate for a primary mass of $25 M_{\odot}$), then its local space velocity would be about 35 km/s, which is also its orbital velocity for

this mass. A velocity of 35 km/s is equivalent to a (maximum) annual proper motion of $\mu = 0.0055''$ at a distance of 1.34 kpc. This is within the error of the (undetected) relative proper motion between ϵ Aur and the centre of Aur OB1, and so one cannot reject the idea that ϵ Aur was born inside the association.

With this conclusion, one can proceed to discuss the evolution of massive stars in connexion with ϵ Aur. Theoretical evolutionary tracks for stars of high mass cross the H-R diagram at roughly constant luminosity three times while the core burns helium. (Some models give only one crossing—occurring at the end of core helium burning—but the distinction is unimportant here.) Because a fossil H II region³³ is not observed around ϵ Aur, it seems likely, though not obligatory, that the primary star is in the second or third post-main-sequence crossing. Mass loss from the stellar surface has virtually no effect on the luminosity or lifetime of the star once the helium core is formed, so the observed luminosity of the primary can be correlated reliably with its original main-sequence mass³⁴. This mass is about $25 M_{\odot}$, as I have assumed. A lower limit on the mass is provided by the mass of the original helium core of $7 M_{\odot}$, for an absence of the hydrogen envelope would prevent the radius expansion necessary to account for the distended characteristic of a yellow supergiant³⁵. Because the percentage of mass actually lost is likely to be slight in the case of a star of such high mass³⁶, a probable value of $25 M_{\odot}$ has been adopted for the primary of ϵ Aur. By using the orbital mass function⁴⁰ of $3.1 M_{\odot}$ and an approximate orbital inclination¹⁷ of 72° , the mass of the secondary comes out to be $19 M_{\odot}$. (In the highly unlikely event of a primary mass of $7 M_{\odot}$, the secondary's mass is $10 M_{\odot}$ —still a very large value.)

In the preceding article Cameron has already assumed that the primary has a high mass and is in a post-main-sequence phase of evolution. Therefore, I accept his necessary conclusion that the secondary must have already completed its evolution and so have had originally a larger mass. The original mass probably did not exceed $60 M_{\odot}$ ³⁸, which then sets an upper limit on how much mass could have been lost through stellar winds, mass exchange and events attending formation of the remnant. By the same token, the lifetime of the secondary in its present state could not have exceeded about 3×10^6 yr. Cameron suggests that the high mass of the secondary is consistent only with the assumption of a collapsar.

It is possible, though unlikely, that a relic of the event which formed the collapsar is the extended radio³⁹ and optical⁴⁰ nebula HB 9 ($l'' = 161^{\circ}$, $b'' = +2.8^{\circ}$). The angular diameter of the nebula is about $2.3''$, and its distance is variously estimated as between 1.1 and 1.9 kpc^{41–43}. The object seems to be a typical type II supernova remnant^{41,44} and so, on this basis alone, is probably derived from a massive star. But there is no known pulsar⁴⁵ or discrete X-ray source⁴⁶ in the general area. There are, however, reasons for rejecting the association of HB 9 with ϵ Aur. HB 9 lies about 2° north of ϵ Aur and on the side of ϵ Aur away from Aur OB1. Furthermore, there is no compelling theoretical reason for a special relic of this nature attending the uninterrupted collapse of a massive object.

If, instead, the bulk of the collapsing star at the initial period of collapse had shrunk to a very small radius while conserving the angular momentum of its outer (or circumstellar) portions by forming a flattened disk of small mass, the disk would be expected to possess the chemical composition and radial extent of the original star just before the collapse. Recent models⁴⁷ indicate that this pre-collapse object would be a cool, highly luminous star with an enveloped enriched in the CNO elements and extending to a radius of, very approximately, $2000 R_{\odot}$. The disk in ϵ Aur has a radius lying in the range 1000 – $4000 R_{\odot}$ (ref. 48, Cameron's article and Kopal's unpublished work) and, quite possibly, a chemical composition of largely graphite if the analogy with 89 Her is adopted as below. It is probably not unreasonable to suppose that most of the gaseous component has been incorporated into grains or else lost owing to

the low gravity. The disk must be moderately thick, or tilted to the orbital plane, in order to produce the observed eclipses. It is understandably very dark, having had possibly millions of years to cool off.

The time scale of collapse of the massive central star to a radius close to the Schwarzschild radius is only a few years. During this time the star radiates away most of its energy in the form of neutrinos and loses its excess rotational angular momentum by the emission of gravitational waves⁶⁰. Theoretical models indicate that no matter is blown off the surface, but that the equivalent mass of emitted neutrinos can be very large⁶¹. Clearly the surrounding disk of solid particles will not be disrupted, because of the virtually noninteracting nature of the star's dominant forms of emission. Subsequent contraction of the central star is very slow (as seen by an external observer), and the star becomes very dim and red, pinching itself off gradually from the rest of the universe⁶⁰.

A third possible interpretation of the luminosity of ϵ Aur is that the evolving system previously suffered mass exchange, suddenly increasing the mass of the primary to $25 M_{\odot}$ at the expense of the mass of the secondary. This would account for the delayed formation of a star of $25 M_{\odot}$ in an association where normal evolution is now taking stars of $20 M_{\odot}$ off the main sequence. It would also account for the paradoxically smaller mass of the more highly evolved secondary. Nevertheless, because the large number of calculated mass-exchange models seem to indicate that the evolving star is always stripped practically down to its core, some mass must have been lost from the system of ϵ Aur as a whole during the exchange process in order to leave a core of $19 M_{\odot}$ in a system which has a present total mass of $44 M_{\odot}$. The large observed separation of $6900 R_{\odot}$ between the components should not necessarily be construed as evidence against any previous mass exchange, because a massive star during the M-supergiant phase can attain an almost comparable radius of $2000 R_{\odot}$, and an exchange of mass at that time might result in the observed separation of the components.

A fourth possible interpretation of the luminosity of ϵ Aur is that the star is actually in the foreground of Aur OB1. Since ϵ Aur lies on the north-west edge of Aur OB1, there is no reason to reject its being also somewhat in front. The total extent of the association perpendicular to the line of sight is about 230 pc, and the projected distance of ϵ Aur from the centre is also about 230 pc. A true distance from the centre equal to approximately twice the transverse extent of the association would be required to bring the luminosity of ϵ Aur down to a value compatible with that of the blue supergiants in Aur OB1. This rather difficult requirement (if ϵ Aur is an association member) means that the original mass of the primary of ϵ Aur could not have been less than about $20 M_{\odot}$.

A further check on the mass of the primary is provided by the average frequency of its irregular fluctuations in light, colour, and radial velocity³⁷, the occurrence of which is not unusual for bright yellow supergiants⁴⁹. If these fluctuations are due to radial pulsation in the fundamental mode (with much interference), then

$$\frac{M}{M_{\odot}} = \left(\frac{L}{L_{\odot}} \right)^{3/2} \left(\frac{T_e}{T_{e\odot}} \right)^{-6} \left(\frac{Q}{P} \right)^2$$

which simply combines the Stefan-Boltzmann law for the surface flux with the definition of the pulsational Q value. Theoretical models^{38,50,51} of supergiants with radiative envelopes are characterized by $Q = 0.04$ day. If one adopts $P = 100$ days, $T_e = 7,000$ K⁵⁷, and $M_{\text{bol}} = -8.7$, the mass of the primary of ϵ Aur turns out to be $6 M_{\odot}$. To appear at the present time as a Ia supergiant, the star must be overluminous for its mass (low surface gravity) and therefore have lost mass at an earlier period, being originally of 10 – $20 M_{\odot}$ (hence still consistent with membership in Aur OB1).

It is not obligatory to conclude, however, that extensive mass loss from the primary has occurred. Rather, to achieve a present mass of $25 M_{\odot}$ for the primary from the expression I

have just given, one might adopt $Q=0.08$ day or $T_e=5,500$ K (both of which are probably unrealistic) or $P=50$ days, which is more realistic in view of the uncertainty of the "period" of the observed fluctuations. Furthermore, the fluctuations may not be due to the fundamental mode of radial pulsation at all. Thus one finds no real contradiction of the preceding result that the primary of ϵ Aur is a massive star of (at least originally) $20\text{--}25 M_\odot$.

Eventually, the faint absorption lines due to the dilute gas surrounding the secondary and appearing in the visual part of the spectrum during eclipse⁵⁰ may be detected outside eclipse as well, leading to a second radial-velocity curve and a direct determination of the masses. Infrared lines might also be sought, although the secondary is known⁵³ not to emit infrared radiation in any appreciable amount at wavelengths shorter than $9.2 \mu\text{m}$.

In this connexion, it may be highly significant that Gillett, Hyland, and Stein⁵⁴ found an unexpected large flux of constant, continuous infrared radiation coming from the otherwise normal F2 Ia supergiant 89 Her. They have suggested that a shell of solid particles at a temperature of $200\text{--}600$ K surrounds the star, which does not seem to share this property with other typical yellow supergiants. An alternative explanation, however, might be that a cool disk of solid particles is surrounding an invisible secondary in a binary system containing 89 Her as the primary; the orbital period is probably rather long, for 89 Her is not known to be a binary. Although radial-velocity⁵⁵ and light⁵⁶ variations in this star have been observed (with a characteristic period of about 70 days), they are clearly not due to orbital effects. The infrared disk of solid particles is assumed here to be associated with an invisible secondary star, rather than to have been accreted from the interstellar medium by an assumed single F star, because 89 Her lies at high galactic latitude where the density of interstellar material is relatively low, and because other yellow Ia supergiants at low galactic latitudes do not show an unexpected infrared excess. The disk in 89 Her must be more massive, or more recently formed, than that in ϵ Aur because of its larger (that is, detected) infrared flux. The model proposed here removes various difficulties encountered by the assumption of a spherical shell around 89 Her: namely, the apparent invisibility of the shell at optical wavelengths, the difficulty of forming solid particles in a relatively hot atmosphere, the lack of similar circumstellar shells around other yellow Ia supergiants that are known to be losing mass (including ϵ Aur⁴⁸), and the probable graphite composition of the radiating particles⁵⁷. Like ϵ Aur, 89 Her seems to have moved considerably from its place of origin⁶⁰, has no listed H II region surrounding it²¹, and is probably an evolved star. No trace of nebulosity around it is seen on the Palomar Sky Survey plates. Furthermore, there is no listed supernova remnant^{41,43}, pulsar⁴⁵ or discrete X-ray source⁴⁶ anywhere near the star, although three unidentified radio sources in the 4C catalogue⁵⁸ have positions nearby. It is therefore quite possible that 89 Her belongs to a new class of stars the prototype of which is ϵ Aur.

In conclusion, there seems to be fairly good reason to believe that the primary of ϵ Aur is a star of high mass which has evolved past the main sequence, being at present in the main phase, or in a peripheral phase, of core helium burning. If this is correct, the massive secondary must be an even more evolved object, and, as Cameron has pointed out, it can really only be a collapsar. A similar object may be in orbit around 89 Her and possibly around other stars that have an unexpected infrared excess. (Perhaps some of the presently unidentified⁵⁹ infrared or OH sources with small angular diameter are also disks containing collapsars, since collapsars are obviously not restricted to binary systems.) The curious infrared excess emitted by these composite objects arises not from the collapsar itself, but rather from the spiralling stream of particles around it.

I thank Dr A. G. W. Cameron for informing me of his work before publication and for stimulating discussions.

Received December 7, 1970.

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LETTERS TO NATURE

PHYSICAL SCIENCES

Symmetric Cosmology

Hoyle¹ and Steigman² have criticized the symmetric cosmology, or rather their personal impression of it. Certain of their statements are incorrect, and we wish to reply to them.

First, without reference or justification they claimed that Klein's metagalactic model turns inside the Schwarzschild limit. This is not correct. A general relativistic treatment of the model has been worked out by Laurent and Söderholm³, who discussed in detail the turning and the Schwarzschild limit.

Second, they claimed, again without reference or justification, that in Klein's metagalactic model the path of photons is long compared with the linear size at the turning. This is not correct. In fact, Klein uses the condition that the metagalaxy must be opaque at the turning to derive Eddington's relations⁴⁻¹¹.

Third, they claimed that we have postulated processes giving rise to magnetic fields of the order of 1-100 gauss. If these values refer to a magnetic field in free space (in a dilute plasma) we have neither explicitly nor implicitly made such an assumption. On the other hand, because stars are known to have fields of the order 50,000 gauss, we have not hesitated to assume that star-like objects have strong fields. In the Ekspong-Yamdagni-Bonnevier ambiplasma mechanism of radio stars¹², fields of the order of 1 gauss are necessary. This mechanism is reconcilable with the ambiplasma model of quasars¹³.

Finally, of the objection in the cited papers the only one to be taken seriously is Woltjers's argument about the general galactic magnetic field. This raises several interesting and difficult problems about antimatter and the galactic structure, and we hope to discuss this later.

The discussion about the symmetric cosmology should not only be focused on the existence of antimatter. An even more essential point in Klein's approach is perhaps to what extent new laws of nature should be postulated. Hoyle has never shown any reluctance to introduce as many new laws of nature as he needs for the moment. In striking contrast to this, the symmetric cosmology can be regarded as an attempt to investigate how far we can understand astrophysics only by the help of laws found in the laboratory. Klein has developed these principles in an article¹¹ which is apparently unknown to Hoyle and Steigman. It should be read by everybody who wants to understand how drastically different Klein's approach is from the continuous creation hypothesis.

We note that Hoyle assumes that "pair creation occurs in the condensed nucleus, and that particles are then expelled away from the nucleus and 'antiparticles' are retained at the nucleus". He does not say by what process such a separation should be accomplished, and seems not to realize that the separation of an ambiplasma is a difficult process, unless a new law of nature is provided to accomplish the separation.

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Received August 21, 1970.

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Possible Newly Recognized Meteorological Phenomenon called Crown Flash

ON July 2, 1970, at about 1945 h EST a thunderstorm cell passed a few miles north of Ann Arbor, Michigan. The column of cumulus cloud towered in the light of the setting Sun, far above the dark mass below, which occasionally flickered with lightning. Thin lamellae of cirriform cloud began to form above the peak of the cumulus column and streamed off to the north-east, in advance of the storm cloud. The cumulus column impinged on these lamellae as it boiled upward, causing the horizontal layers of thin cloud to become somewhat dome-shaped in the region of the rising column (Fig. 1). At and just above the peak of the storm cell the cloud mass seemed to be undergoing sudden changes in brightness lasting for several seconds at a time. J. C. G.'s wife and two children also noticed the effect when it was called to their attention. M. E. G., a meteorologist, also verified the observation. The phenomenon continued to occur repeatedly at intervals of 30-60 s during the next 15 or 20 min, providing the basis for the following description.

The sudden brightening effect began concurrently with lightning strokes in the main cloud mass, but continued after the lightning flash was over. It had the appearance of a ripple-like upward and outward spread of radiance from the region just west of the peak of the cumulus column, resembling somewhat a fan-like display of aurora borealis. It lasted a substantial fraction of a second with each lightning stroke. On one or two occasions it had the appearance of a bright ring moving rapidly outward and upward above the cumulus peak. On these occasions it was clearly observed to extend beyond the cloud and into blue sky. A linear shadow, apparently cast by one of the cumulus masses, appeared to shift its position suddenly up or down with each occurrence of the event (Fig. 1a).

While the effect was observable, the portion of the cloud mass most immediately involved seemed considerably brighter than the remainder of the cumulus peak, which was still in sunlight. This area of the cloud seemed to glow from within; the individual puffs of cumulus cloud did not seem to cast shadows but glowed with equal intensity in all portions; the zones between puffs were not dark as in the remainder of the cloud, but bright as if light were escaping through them. The colour of the entire phenomenon was white.

Hourly radar log reports from Detroit Metropolitan Airport,

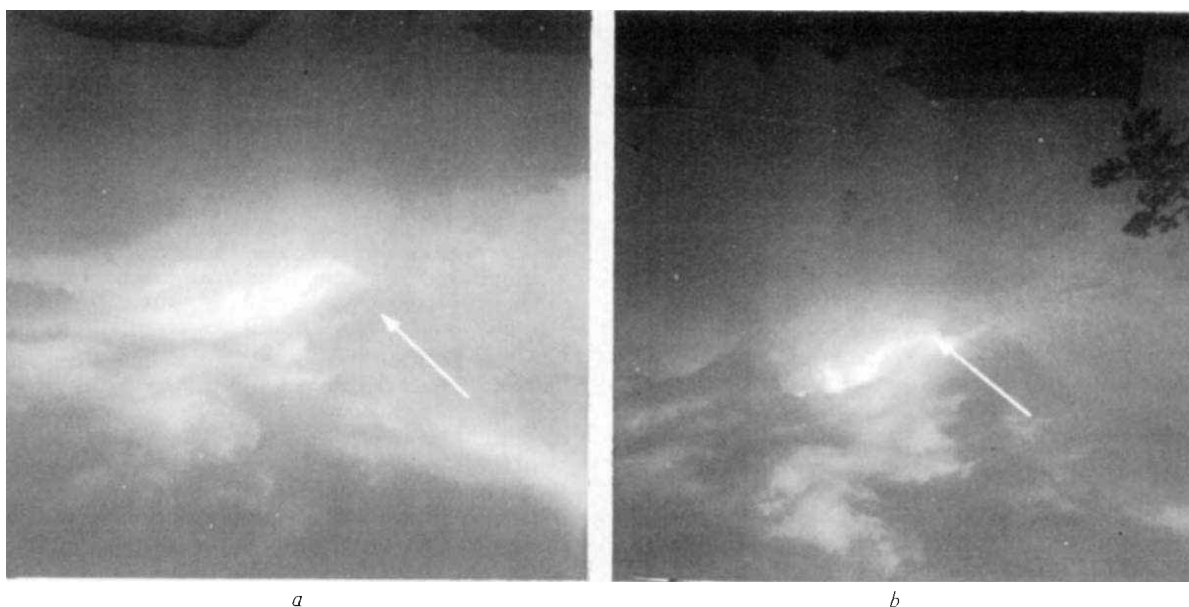


Fig. 1 Cloud mass as it appeared during the crown flash: (a) at approximately 1950 h EST, and (b) at approximately 2005 h EST. Arrows indicate the region in which the effect was observed. Tip of arrow in a denotes linear shadow referred to in text. (Original photographs taken in colour with a simple box camera.)

24 miles ESE of Ann Arbor, for the evening of July 2, 1970, were later consulted. At 1900 h radar echoes were reported 117 miles due west of the airport, moving from the WNW (290°) at 25 knots, with prominent peaks at 50,000 feet and containing 0.75 inch hail. At 2000 h, echoes with peaks at 45,000 feet were recorded 90 miles due west of the airport. At 2100 h, large storm cells with peaks at 40,000 feet were recorded in the Ann Arbor area. Official sunset occurred at 1941 h EST on that day.

We speculated that the phenomenon observed represented some sort of ionization discharge, perhaps occurring at the top of a column of ionized air associated with the thunderhead. Conceivably, the effect tends to occur in favourable conditions of rapid updraught with strong winds aloft, associated with a relatively energetic thunderstorm. If so, it may represent one early stage in the formation of a vortex that could eventuate in production of a tornado¹.

We have been unable to find published reports describing a similar phenomenon. We invite readers who may know of such published reports, or who may have observed similar effects themselves, to communicate their findings. We have tentatively designated this phenomenon the "crown flash".

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Received August 17, 1970.

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Scattering of Two Impulsive Gravitational Plane Waves

It has long been recognized that Einstein's gravitational equations admit wave-like solutions. But because of the smallness of the gravitational constant it would require an exceedingly violent astronomical process to generate gravitational waves of sufficient intensity to be detectable with available apparatus. Weber¹⁰ has, however, presented a plausible case

for believing that his detectors may indeed have monitored frequent and sharply pulsed gravitational waves, which seem to be emanating from the centre of our galaxy. Because such waves could give some very significant information about extraordinary processes which may be taking place in certain regions of the universe, the detection of gravitational waves may be important in the observational astronomy of the future.

Unlike the waves of standard electromagnetic theory, however, gravitational waves cannot generally be superposed linearly, except in the weak field limit. A significant theoretical requirement, therefore, is to determine the way in which gravitational waves can scatter one another. But so far, rather little is known about the detailed nature of this scattering. The purpose of this communication is to try to remedy this situation to some degree. We shall present, for the first time, an exact solution of Einstein's vacuum equations representing a collision between two impulsive (δ -function) gravitational plane waves. This facilitates detailed examination of the scattering for this case.

The metric

$$ds^2 = dU\{2dV + (Y^2 - X^2)h(U)dU\} - dX^2 - dY^2 \quad (1)$$

due originally to Brinkmann², and interpreted by Robinson⁸, represents a linearly polarized gravitational plane wave. The amplitude function $h(U)$ can be given arbitrarily, its second X and Y derivatives defining the curvature of the space-time. Two such waves moving in the same direction can be superposed, simply by adding their corresponding h functions. Thus, when moving in the same direction, two such gravitational waves do not scatter one another.

To exhibit scattering we need waves moving in different directions. If we consider sandwich waves¹, we can match together the regions of flat space which precede each of the two waves. For this, the Rosen⁹ form of the metric is more convenient than equation (1). By means of the coordinate change⁸ $U = u$, $V = v + \frac{1}{2}x^2FF' + \frac{1}{2}y^2GG'$, $X = xF$, $Y = yG$, where F and G are functions of U subject to $F'' = hF$, $G'' = -hG$, we obtain Rosen's form

$$ds^2 = 2Ldu dv - F^2 dx^2 - G^2 dy^2 \quad (2)$$

(with $L=1$). If $F=1+u\theta(u)$ and $G=1-u\theta(u)$, where $\theta(u)$ is Heaviside's step function, we get the "impulsive wave"⁶ for which $h(u)=\delta(u)$. Now, by allowing L , F and G to be func-

The primary flux of charged particles, from the magnetic polar caps, is believed to be highly bunched, the period between bunches being comparable with the time it takes light to travel across a polar cap. For the Crab pulsar, the radius of the polar cap is estimated to be 10^5 cm, so that the basic modulation frequency will be of order $3 \cdot 10^5 \text{ s}^{-1}$. It seems likely that the flux of secondary particles will exhibit a modulation similar to (but probably smaller than) that of the primary flux. If so, this modulation should be evident in the optical and other radiation.

The flux of light received from the Crab pulsar is such that about sixty photo-electrons are produced in each main pulse at a photo-multiplier attached to a 100 inch telescope². The pulse width is about 3 ms, and so the average inter-arrival time is about 50 μs . If one assumes that the modulation frequency probably lies between 10^5 s^{-1} and 10^6 s^{-1} (so that one should search over this range), the average inter-arrival time is between five and fifty times the modulation period. Thus it would be impossible to detect the high frequency modulation by a direct method such as a filter-detector combination attached to the photomultiplier output.

If the modulation were strong, however, it would be possible to detect the modulation by forming a histogram of photo-electron inter-arrival times³. To search over the proposed range of frequencies, inter-arrival times should be measured to substantially better than 1 μs , say to 0.2 μs . Inter-arrival times might be measured directly, by appropriate circuitry or by analysis of photo-electron arrival times, which must then be recorded with an accuracy of about 0.1 μs .

It should be noted that the pulse and inter-pulse of the Crab pulsar originate at opposite magnetic poles and that there is no reason to expect that opposite poles will exhibit oscillations at exactly the same frequency. Thus it is necessary to accumulate and analyse data separately for the main pulse and for the interpulse.

If there is no high frequency modulation, a histogram of inter-arrival times will be exponential, with an e-folding time equal to the average inter-arrival time, which we take to be 50 μs . Thus it would seem reasonable to sort inter-arrival times over the range 0 to 40–200 μs , using 200–1,000 bins of width 0.2 μs . (This number can be adjusted to meet the capabilities of available equipment.) If there is high frequency modulation, this should show up as a periodic modulation superimposed on the exponential. The number of oscillations which can be detected would be a measure of the "Q-factor", and hence indicate the band-width, of the oscillator. If the signal has a small depth of modulation of (fractional) amplitude δ_s , and of well-defined frequency ($Q \gg 1$), then the histogram will have a depth of modulation δ_H , for time-delays small compared with the mean inter-arrival time, where

$$\delta_H \approx 1/2 \delta_s^2 \quad (1)$$

If one aims at detecting a 1% modulation of the histogram in any one low-numbered bin, corresponding to a 14% modulation of the signal, it will be necessary to accumulate substantially more than 10^4 counts per bin, say 10^5 counts. Because only one out of 250 inter-arrival times has a value of 0.2 μs or less, it is necessary to count 2.5×10^7 inter-arrival times, or 4×10^5 pulses. This amount of data can be accumulated in about 4 h. It seems, therefore, that modulation, if it exists with parameters comparable with those proposed, should be detectable.

If inspection of the inter-arrival-time histogram indicates the presence of modulation, it would be desirable to carry out a statistical test for the validity of this inference. Although tests could be applied to the inter-arrival-time histogram, a simpler and more direct test can be applied to the photo-electron time series, as follows.

Divide the duration of each pulse into "bins" of size $1/2 \tau$, where τ is the period indicated by the modulation of the inter-arrival-time histogram, using a random phase selection for each pulse. For pulse number i , let $N_{0,i}$, $N_{E,i}$ be the total

number of photo-electrons counted in the odd-numbered bins and even-numbered bins, respectively. Then the data for pulse i lead to the following estimate $\Delta_{H,i}$ for the depth of modulation δ_H :

$$\Delta_{H,i} = 1.5 \frac{(N_{0,i} - N_{E,i})^2 - N_i}{N_i^2} \quad (2)$$

where

$$N_i = N_{0,i} + N_{E,i} \quad (3)$$

Combining data from all pulses, $i = 1, \dots, P$, one arrives at the following estimates of the depth of the modulation and of the standard deviation:

$$\Delta_H = P^{-1} \sum_{i=1}^P \Delta_{H,i} \quad (4)$$

$$\sigma_H^2 = P^{-2} \sum_{i=1}^P (\Delta_{H,i} - \Delta_H)^2 \quad (5)$$

Estimates Δ_H for the depth of modulation δ_H , obtained in the above manner, will be normally distributed (asymptotically in P) with standard deviation estimated by σ_H . Thus one can set confidence limits on possible ranges of values of δ_H , using standard statistical tables. For example, the following range is given with 95% confidence:

$$(\Delta_H - 1.96\sigma_H) < \delta_H < (\Delta_H + 1.96\sigma_H) \quad (6)$$

If this range excludes the value $\delta_H = 0$, the hypothesis $\delta_H = 0$ is rejected with 95% confidence.

Although, for definiteness, details have been quoted for observations made with a 100 inch telescope, the test could be made with a smaller telescope if photo-electrons are accumulated over a longer period of time. If the photo-electron rate is smaller than that quoted by a factor f , the mean inter-arrival time will be larger by a factor f^{-1} . In consequence, it is necessary to count f^{-2} times as many pulses in order to accumulate the specified numbers of counts in each bin.

This work was supported in part by the Air Force Office of Scientific Research.

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Received November 19, 1970.

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Experiment to detect Pulsed γ -Rays from the Crab Nebula

A BALLOON-BORNE experiment using a telescope sensitive to γ -radiation between 10 and 150 MeV was successfully flown on October 25, 1969, from Palestine, Texas, and was oriented to within 2° of the Crab Nebula. Preliminary results indicate an enhanced response in phase with the optical pulses and with an intensity close to that predicted from an extrapolation of the total X-ray emission from the Crab.

The telescope is shown in Fig. 1. γ -Rays are detected when they interact in a nuclear emulsion stack (650 cm², 0.6 radia-

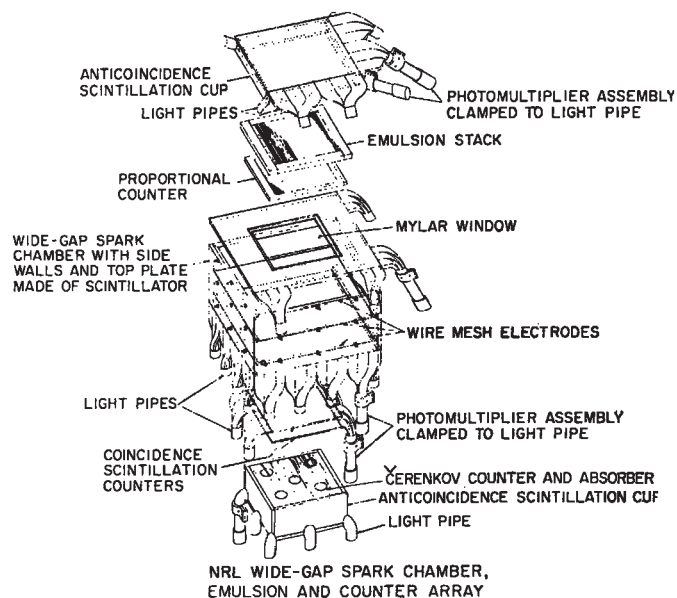


Fig. 1 Diagram of the γ -ray telescope.

tion length) producing electron pairs or Compton recoil electrons which traverse a multi-wire proportional counter and a pair of plastic scintillation counters. An upper energy limit is placed on the electrons by requiring that they stop in a five-inch thick block of clear plexiglas placed below the two scintillation counters. The block also serves as a Čerenkov counter to reject upward-coming γ -rays converting in it. Phototubes embedded in the block view the Čerenkov light from a diffuse reflector placed above it. Charged particles are rejected by plastic scintillators covering a solid angle of close to 4π . When a γ -ray is detected by the telescope, a spark chamber consisting of two four-inch gaps is actuated. Sparks are recorded in 90°-stereo on 35-mm film.

In a complete analysis of the experiment, the electron tracks are located in the nuclear emulsion from measurements made on the sparks. These tracks are then followed back to the γ -ray interaction. The direction of an incident γ -ray can then be determined to within $\sim 2^\circ$ at 20 MeV and its energy to ~ 25 per cent. This stage of analysis is currently in progress. Our preliminary investigation, upon which this report is based, involves measurements made only on the spark chamber photographs.

We have calculated the telescope's sensitivity within a range of γ -ray energies using Monte Carlo techniques and have also measured it at ~ 50 MeV at the NRL Electron Linac. There is good agreement between the measurement and calculation. Sensitivity begins for photons with energies above 10 MeV and increases up to a maximum efficiency of about 11 per cent for photons between 50 and 60 MeV incident at 0° ; it then decreases gradually, falling to below 1 per cent by 150 MeV.

Only 30 per cent of the γ -ray events from the Crab observed in the spark chamber are expected to show the two electron tracks characteristic of the pair production process. The rest will show only a single electron track, and these include the cases when: (a) one of the members of a pair stops in the emulsion and (b) the second track is not visible in the spark chamber because of spark robbing, or (c) the γ -ray produces a Compton electron. Our analysis therefore includes events in which a single electron is visible as well as those showing an electron pair.

The telescope reached a float altitude of 4.3 g cm^{-2} at 07.45 UT. Photographs of 8,500 events were obtained of which 901 were downward moving electron pairs produced by γ -rays interacting in the emulsion stack. The rest consisted mostly of single tracks of which about 50% are identified by their scattering ($>1^\circ$) in the spark chamber gas (90% neon, 10% helium)

to be electrons with energy $\gtrsim 5$ MeV. These soft electrons are attributed to the intense flux of albedo γ -rays, some of which convert in the plexiglas block but are not rejected by the Čerenkov counter and stop in the emulsion stack. The remaining straight single tracks are predominantly electrons originating from downward moving γ -rays interacting in the emulsion stack. Only electron pairs and straight single tracks are included in our analysis.

Data were telemetered in real time to the primary receiving station in Laurel, Mississippi, and a secondary station in Palestine, Texas. Pulses marking the detection of a γ -ray event were recorded on magnetic tape at both stations. At the Laurel station a clock with a stability of ~ 3 parts in 10^{10} generated 1 Hz and 5 kHz timing markers which were superimposed on the same tape channel as the event pulses. At the Palestine station a 10 kHz oscillator with a drift of 0.4 ms h^{-1} was used. The r.m.s. difference in arrival times of events recorded at the two stations was $\gtrsim 0.3 \text{ ms}$ after corrections were made for oscillator drift and balloon trajectory. Universal time was determined from station WWV and confirmed with an uncertainty of $< 1 \text{ ms}$ by calibration of the high stability clock with the US Naval Observatory and NRL standards. Correlation between the film and telemetry data was made possible by an Accutron clock which appeared on each photographic frame.

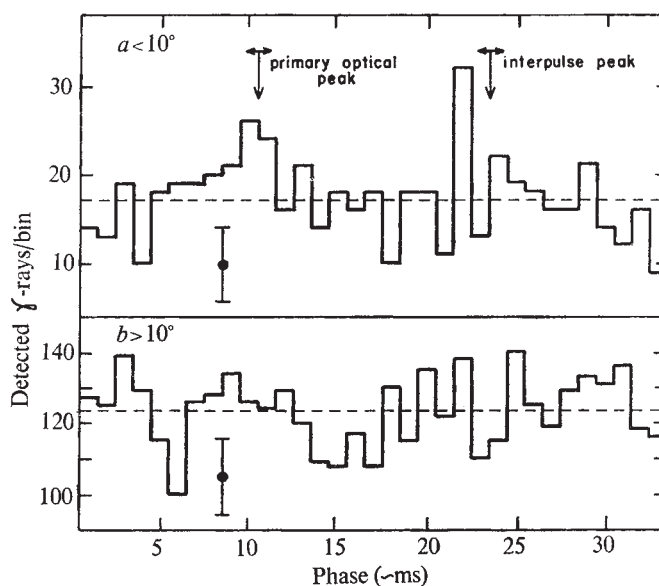


Fig. 2 γ -Ray data (straight single tracks and pairs) as a function of phase for NP 0532. a, Events pointing within 10° of the Crab; b, events pointing greater than 10° from the Crab. The dashed lines represent the mean number of γ -rays per bin; the error shown is one standard deviation for a bin having the mean number of events.

We obtained the apparent period and phase of the optical emission of NP 0532 for the day of the flight from the Smithsonian Institution Astrophysical Observatory and Harvard University. (The period was obtained by Dr D. R. Hearn and Dr G. G. Fazio, and also by Dr P. Murdin (University of Rochester). Data on the optical phase were provided by Dr P. Horowitz, C. Papaliolios and N. P. Carleton.) At 07.30 UT on October 25, 1969, the apparent period at the Laurel, Mississippi, ground station was 33.1010909 ms and a primary peak occurred at 7 h 30 m 0.0065 s UT. Corrections were made for the transit time between the balloon location and Laurel, and each event photographed was assigned a phase relative to the pulsar's period.

In this preliminary stage of our analysis, we are limited in angular resolution by scattering of electrons in the emulsion

prior to their entering the spark chamber. This has the undesirable effect of burying γ -rays from the Crab in the intense atmospheric background. With the aid of our Monte Carlo calculation, we have found that, by considering only electron pairs and straight single electron tracks ($\lesssim 5$ MeV) in the spark chamber whose measured directions were within 10° of the Crab, we could optimize the probability of detecting the source. This sample should contain 50 per cent of γ -rays detected from the Crab but only 15 per cent of the atmospheric background.

In Fig. 2a we plot the arrival time distribution for events $< 10^\circ$ from the Crab and in Fig. 2b the distribution for events $> 10^\circ$. We have marked the locations of the optical peaks. Two features stand out for γ -rays arriving at less than 10° from the Crab. The first is an excess of events in a 2 ms interval coincident with the primary optical peak, and the second an excess in a 1 ms interval about 1.5 ms before the interpulse peak. The probabilities of obtaining the excesses at these locations from a random distribution are 0.006 and 0.0008 respectively. We performed χ^2 analyses on the $< 10^\circ$ distribution first grouped according to the detailed pulse structure observed in low energy X-rays¹⁻³, and second, divided into a 14 ms background region (bins 27-33 and 1-7) and 19 ms pulsed region. These analyses gave values of χ^2 greater than those obtained in 99 per cent and 98 per cent, respectively, of distributions generated randomly.

We consider this result to be probable, but not conclusive, evidence for pulsed γ -radiation > 10 MeV from the Crab pulsar. We estimate the flux of γ -rays from the observed excess within ± 1 ms of the primary optical peak and $\pm \frac{1}{3}$ ms of the interpulse (this reflects the slow rise and fast fall observed in X-rays) compared with the "background" assumed to be contained in bins 27-33 and 1-7. The estimated flux of pulsed γ -rays is dependent upon the assumed energy spectrum. For an E_γ^{-2} differential spectrum we obtain $4.0 (\pm 2.5) \times 10^{-4} \gamma \text{ cm}^{-2} \text{ s}^{-1}$ for $E_\gamma > 10$ MeV (the uncertainty is primarily statistical).

An extrapolation of the total X-ray emission of the Crab⁴ to γ -ray energies, which is consistent with the upper limit⁵ to the flux above 50 MeV, yields an expected flux of $\sim 10^{-4} \text{ cm}^{-2} \text{ s}^{-1}$ above 10 MeV. Should our measurement be confirmed it would indicate that the pulsed component dominates above 10 MeV. At X-ray energies (1-10 keV), the ratio of pulsed to total emission has been observed^{1-3,6} to be increasing sharply with energy. The same ratio between 10 and 200 keV seems to remain constant at ~ 0.15 , however^{3,7,8}. At higher energies (0.6-9 MeV) there is recent evidence from unpublished work of R. R. Hillier *et al.* that this ratio again increases⁷. Possible observations of pulsed γ -rays > 50 MeV with a flux $\sim 10^{-5} \text{ cm}^{-2} \text{ s}^{-1}$ were recently reported⁹; these results have subsequently been questioned^{10,11}.

We are proceeding with the final phase of our analysis involving those γ -ray interactions which can be located in the emulsion. Measurements on these events will improve the angular resolution to $< 2^\circ$ above 20 MeV. With this resolution, the telescope has a sensitivity of $\sim 10^{-5} \gamma \text{ cm}^{-2} \text{ s}^{-1}$.

We thank Dr M. M. Shapiro, who initiated our γ -ray astronomy programme, for advice and support. We also thank J. Harmon, O. Rhue, P. Richardson, R. Wilkinson, S. Highley, C. Kennedy, and J. O'Neill for technical support, J. Silverman, H. Shapiro, and S. Cohee for film scanning, W. Nagel of NASA for the pointing controls, Dr R. G. Glasser for discussions, and the personnel of the NCAR Balloon Facility for flight operations.

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Iceberg Tracking off Labrador

LITTLE is known about the rate and direction of the drift of icebergs in the Labrador area of the continental shelf. Because of the obvious hazard to offshore drilling operations in this potentially oil-rich area there is an urgent need for detailed information. We wish to report the results of an operation carried out by Maritime Command of the Canadian Armed Forces, in cooperation with the Defence Research Board of Canada.

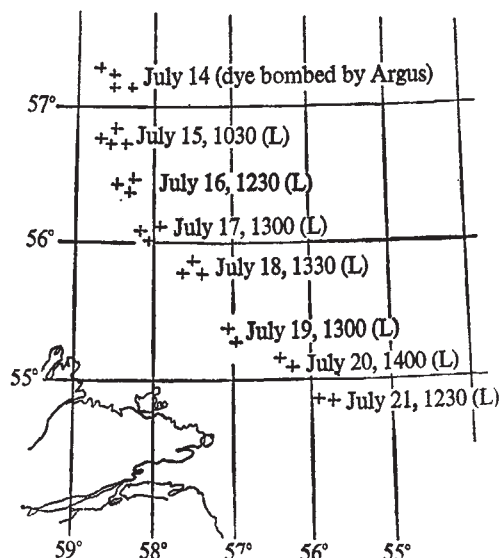


Fig. 1 Positions of icebergs as located and marked by Argus aircraft and plotted by Tracker aircraft, July 14-21, 1970.

A group of four icebergs was marked by dropping dyed sand enclosed in thin cardboard containers from Argus and Tracker aircraft onto the icebergs. Each impact produced a small stained area, and there were several on each marked iceberg. These stains were sufficient to allow positive identification of the icebergs during a period of several days.

After the initial marking, icebergs were tracked by Tracker aircraft flying from Goose Bay, Labrador. Navigation errors were kept to a minimum by detailed corrections on the return flight, the probable error being not more than one or two miles. This is to be compared with measured drift rates of twenty-five miles d^{-1} . One of the original four icebergs was lost on the third day and a second on the sixth day of tracking presumably as a consequence of overturning. Details of the located posi-

Table 1 Positions for the Icebergs shown in Fig. 1

July 14	Icebergs (4) bombed by Argus A/C	July 18	Time 1330 (L)
Positions	57:20N 58:50W 57:15N 58:40W 57:05N 58:30W 57:05N 58:15W	Positions	55:47N 57:25W 55:40N 57:32W 55:37N 57:20W
July 15	Icebergs (4) relocated by Tracker A/C. Time 1030 (L)	July 19	Only two icebergs found. Time 1300 (L)
Positions	56:48N 58:35W 56:45N 58:45W 56:45N 58:40W 56:43N 58:30W	Positions	55:20N 56:58W 55:18N 56:52W
July 16	Only three icebergs found. Time 1230 (L)	July 20	Time 1400 (L)
Positions	56:30N 58:10W 56:25N 58:25W 56:21N 58:15W	Positions	55:10N 56:30W 55:08N 56:25W
July 17	Time 1300 (L)	July 21	Time 1230 (L)
Positions	56:05N 58:08W 55:59N 59:01W 56:07N 57:55W	Positions	54:55N 56:05W 54:52N 56:00W

tions and times are shown in Table 1, and the approximate track is shown in Fig. 1.

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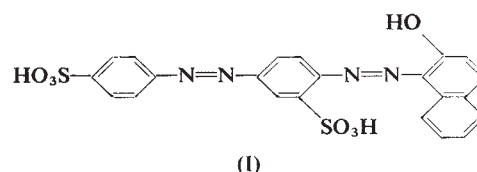
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Dimerization of Biebrich Scarlet and the Monomer- α -Chymotrypsin Interaction

A CONVENIENT method for following the binding of a colourless competitive inhibitor I_1 to an enzyme is to use a second, coloured, inhibitor I_2 which is known to bind at the active site. If a spectral change is associated with the interaction between I_2 and the enzyme, the gradual replacement of I_2 as successive amounts of I_1 are added to a mixture of it and the enzyme can

be demonstrated. The acridine dye, proflavin, has been used in this way¹ with α -chymotrypsin, and it has been suggested that the spectral change can be used to follow conformational changes at the enzyme site during the catalytic process. The azo-dye Biebrich scarlet (I)



can be used similarly with, for example, α -chymotrypsin² and lysozyme³.

The binding of Biebrich scarlet (BS) to α -chymotrypsin was first reported by Glazer², who measured the dissociation constant spectrophotometrically on the assumption that BS does not dimerize at concentrations below 10^{-4} M. This assumption was based on an approximate linearity of a Beer's law plot, although a spectral difference was noted between a solution of 3×10^{-5} M (in a 1 cm cell) and one of 3×10^{-4} M (in a 0.1 cm cell), indicating self-association of the dye at concentrations greater than about 10^{-4} M. The work of Winkelman and Spicer⁴ had also suggested that the self-association of BS was insignificant below 10^{-4} M. We have used the technique of temperature-jump relaxation spectrometry to study the binding of BS to α -chymotrypsin and have evidence for the dimerization of BS even at total concentrations as low as 1.2×10^{-5} M.

In the temperature-jump relaxation technique, a very rapid heating pulse is applied to a system in which the position of equilibrium is temperature-sensitive and the resultant spectral change is followed. In two important respects it is a more sensitive method than conventional spectrophotometry for the detection of small spectral changes of the type involved here. First, the optical system is designed to study very small changes in absorbance, especially in conditions such that absolute absorbance is high (for example 0.7–1.0). Second, consecutive reactions can be separated along the time axis. This is particularly useful in the study of the interaction between BS and α -chymotrypsin because we can then show that the comparatively small absorbance difference at a given wavelength between a mixture of BS and the enzyme, and the free BS, represents two considerably larger differences: an increase in absorbance and a decrease.

The relaxation behaviour of a mixture of BS (1.0×10^{-4} M) and α -chymotrypsin (8.0×10^{-4} M) at 545 nm on different scanning time bases is shown in Fig. 1. The first relaxation

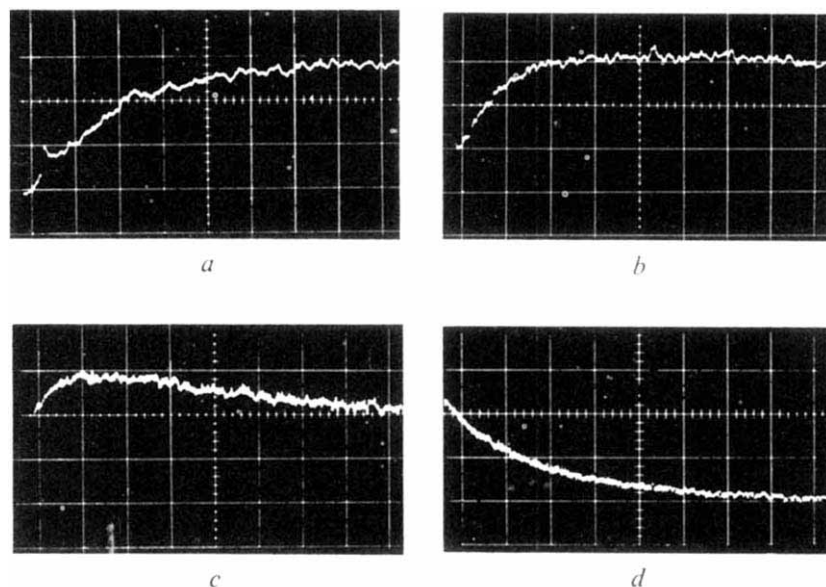
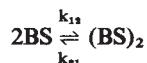


Fig. 1 A typical temperature-jump relaxation spectrum of the Biebrich scarlet- α -chymotrypsin system at 545 nm. Time bases are: a, 10 μ s; b, 20 μ s; c, 50 μ s, and d, 500 μ s per large division and the sensitivity is 20 mV per large division in each case. Conditions: 1.0×10^{-4} M total BS, 8.0×10^{-4} M total α -chymotrypsin; pH=8.5 (Tris/HCl); ionic strength=0.2 M (KNO_3); temperature rise, 2.9° C, final temperature=13.3° C.

(Fig. 1a) is attributed to the dimerization of BS :



The slower relaxation (Fig. 1b) is attributed to the binding of monomeric BS to CT at the active site :

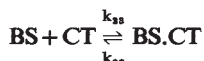


Fig. 1b and c, taken on intermediate time bases, show the gradual disappearance of the dimerization and the appearance of the enzyme-binding behaviour.

This interpretation is supported by the observation that solutions of BS of the same total concentrations as non-enzyme-bound BS in the BS + α -chymotrypsin system gave relaxation effects in the same direction and with the same time constant as the fast effect in the corresponding enzyme-containing solutions. The dependence of τ^{-1} on total BS concentration (1.2 – 3.7×10^{-5} M) in the absence of enzyme was used to determine k_{12} and k_{21} by means of an iterative computer program. At 20° C and an ionic strength of 0.1 M (Tris buffer, KNO_3) the values $1.5 (\pm 0.2) \times 10^9 \text{ l. mol}^{-1} \text{ s}^{-1}$ and $1.3 (\pm 0.3) \times 10^4 \text{ s}^{-1}$, respectively, were obtained (corresponding to a dimerization constant of $1.2 \times 10^5 \text{ l. mol}^{-1}$). They were found to be independent of pH in the range 6–9 (the pK_a of BS in these conditions being > 11). A second, slower and very much smaller, relaxation effect was observed at higher concentrations, probably associated with a further aggregation reaction; this was not studied further.

The rate constants k_{12} and k_{21} determined in the enzyme-free system were used in an analysis of the relaxation times determined for the BS- α -chymotrypsin system. A computer-fit of the data obtained at 20° in solutions of α -chymotrypsin (2 – 12×10^{-5} M) and BS (1 – 3×10^{-5} M) at pH 7.6 (phosphate buffer) and ionic strength 0.3 M (KNO_3) gave k_{23} and k_{32} values of $2.1 (\pm 0.2) \times 10^7 \text{ l. mol}^{-1} \text{ s}^{-1}$ and $6.6 (\pm 0.4) \times 10^2 \text{ s}^{-1}$, respectively (corresponding to an equilibrium constant of $3.2 \times 10^4 \text{ l. mol}^{-1}$). The rate constants were dependent on ionic strength. Further relaxation effects in the ms–s time region were observed which could be attributed to conformational changes of the enzyme. This work will be reported in greater detail in a later publication.

Our observations indicate that, even at 3×10^{-5} M total BS, the amount of free monomer is only about a third of the total. They also suggest that it would be rather difficult to use Biebrich scarlet to monitor enzyme conformational changes taking place in the 10 – $500 \mu\text{s}$ time range.

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Crystal Structure of $\text{Cu}(\text{adenine})_2\text{Cl}_2 \cdot 3\text{H}_2\text{O}$ and Bridging Capability of Adenine

THE observation¹ that copper(II) ions reversibly denature DNA has stimulated interest in the type of bonding between these metal ions and the nucleotide bases adenine, cytosine, guanine and thymine. The interaction between these bases and metal ions by the formation of coordinate bonds would have a marked effect on the key hydrogen bonds in the biological systems. In the case of adenine (Ade) it is known² that various cupric salts will form compounds of the stoichiometries $\text{Cu}(\text{Ade})_2\text{X}_2 \cdot n\text{H}_2\text{O}$ and $\text{Cu}(\text{Ade})\text{X}_2 \cdot n\text{H}_2\text{O}$, and an inner complex $\text{Cu}(\text{C}_5\text{H}_4\text{N}_5)_2 \cdot 4\text{H}_2\text{O}$ can also be isolated. This last compound has an interesting dimeric structure³ in which pairs of copper ions are held $2.947 \text{ \AA}$ apart by four bridging adenine anions, coordinated through N(3) and N(9). Magnetic and electron proton resonance (EPR) studies⁴ have shown that there is pronounced antiferromagnetic coupling between the two copper atoms.

Results from two laboratories have revealed^{5,6} that the complexes $\text{Cu}(\text{Ade})_2\text{X}_2 \cdot n\text{H}_2\text{O}$ also show spin coupling behaviour for a range of anions X, and it has been suggested^{5,6} that the dimeric unit found for the inner complex is retained in the $2:1$ compounds even though the presence of the anions would, in most cases, permit the formation of alternative, more common coordination geometries. This fact, and the continuing problem of the origin of the spin-coupling in copper(II) dimers⁷, has led us to examine the structure of one of these compounds, $\text{Cu}(\text{Ade})_2\text{Cl}_2 \cdot 3\text{H}_2\text{O}$, by single-crystal X-ray methods.

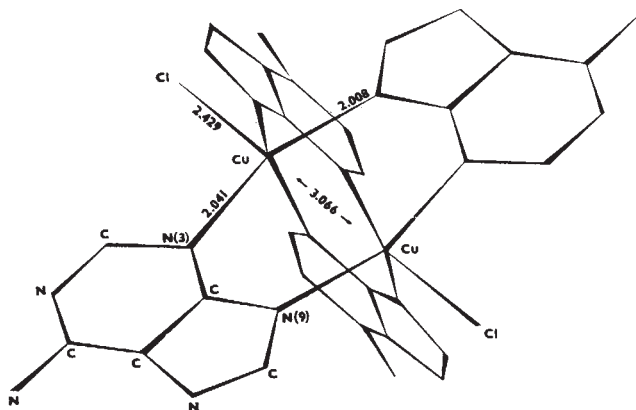


Fig. 1 The $[\text{Cu}(\text{Ade})_2\text{Cl}]_2^+$ ion. Standard deviations are: Cu...Cu, 0.004 ; Cu-Cl, 0.006 ; Cu-N, $0.011 \text{ \AA}$.

The compound crystallizes from water as blue-green plates which are orthorhombic. The unit-cell dimensions are $a = 23.92$, $b = 13.844$, $c = 11.262 \text{ \AA}$, $U = 3729 \text{ \AA}^3$, $D_m = 1.66$, $Z = 8$, $D_c = 1.63$, space group $Cmca$. The structure has been determined from 870 independent reflexions, obtained with Cu-K α radiation and visually estimated. Least-squares refinement has now reached $R = 0.099$. (Atomic coordinates can be obtained on request to A. C. S.).

The structure contains the complex cation $[\text{Cu}(\text{Ade})_2\text{Cl}]_2^+$, chloride ions, and molecules of water of solvation. The dimeric cation, which has $2/m$ crystallographic symmetry, is shown in Fig. 1. The Cu...Cu separation of $3.066 \text{ \AA}$ is appreciably larger than that found in the dimeric inner complex³. Because of this the tetragonal pyramidal coordination about the copper is more distorted with the metal atom $0.33 \text{ \AA}$ above the plane of the four nitrogens. The Cu-N bond lengths are very similar in both complexes.

The chloride ions together with the water molecules and all non-donor nitrogen atoms of the adenine form an intricate

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network of hydrogen bonds, in which bonds of the type O-H...N, N-H...O and O-H...Cl⁺ are involved.

In view of the fact that virtually all other copper complexes of the type CuL₂X₂ (L=a heterocyclic amine, X=Cl or Br) have tetragonal planar, polymeric halide bridged, or distorted tetrahedral coordination geometries, it is significant that the dimeric unit found in the adenine inner complex persists in the compound Cu(Ade)₂Cl₂·3H₂O. From the available e.p.r. and magnetic evidence^{5,6} this is now almost certainly true for several other Cu(Ade)₂X₂·nH₂O compounds, though in some of them water molecules and not anions will occupy the terminal coordinate positions. The key bridging arrangement of donor atoms in adenine is found in several other molecules of biological significance, so systems containing closely held and electronically interacting pairs of metal ions may be more widespread than has been realized hitherto.

Finally, we note that although the extent of spin-coupling in the compound under discussion is comparable with that in copper acetate ($\mu_{\text{eff}} = 1.45$ BM at 295 K) the relatively long Cu-Cu distance of 3.066 Å reinforces the conclusion drawn previously⁵ that the spin coupling in copper dimers of this type proceeds predominantly via a superexchange mechanism involving the bridging groups, and not by any significant direct metal-metal bonding.

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Received June 16; revised September 1, 1970.

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B₂O₃ ~13 wt.%. The oxide ratios are thus 4.01 : 1.07 : 1.00, which are close to the ideal 4 FeO·Fe₂O₃·B₂O₃ or approximately Fe₂" Fe''' BO₅.

The experimental work involved coating a clean, polished iron surface with ortho-boric acid at room temperature, after which the sample was oxidized in pure oxygen in the temperature range 700°–1,100° C. At 480° C, ortho-boric acid had fully transformed to a melt of boric oxide, which dissolved the initial oxide film. In the continuing oxidation process, reactions between the melt and iron oxides produced a solid, multilayered scale structure.

Metallographic evidence indicated that the innermost scale layer (~40–100 μm thick) comprised a granular structure associated with extensive void formation. The layer became increasingly disrupted as the temperature of oxidation was increased. The remainder of the scale structure was mainly wüstite with a thin, outermost layer of magnetite. At 1,100° C, a thin, outer layer of haematite was observed above the magnetite. The microhardness of the inner granular layer was of the same order as that for magnetite. No evidence of a "glassy" phase or residual boric oxide was observed.

Electron probe microanalyses of the inner layer revealed a composition of 65.2 wt.% iron, 30.3 wt.% oxygen and, by difference, the remaining 4.5 wt.% was assumed to be boron. This analysis corresponded closely to the theoretical composition of iron boro-ferrite (vonsenite) containing 64.8 wt.% iron, 30.9 wt.% oxygen, 4.3 wt.% boron. X-ray evidence from powdered, detached scales indicated lattice parameters which were in close agreement with published data⁵ for ortho-rhombic iron boro-ferrite.

The ortho-boric acid coating was found to decrease the oxidation rate of high purity iron. The determination of oxidation kinetics from thermogravimetric data supported the hypothesis that the porous vonsenite layer at the scale/metal interface forms a "blocking layer" which restricts diffusion. The effective surface area for diffusion of iron ions in wüstite is therefore, decreased. The "blocking" effect seems to be enhanced by the extensive voids associated with the vonsenite layer. Work is in progress to clarify the constitutional and reaction kinetic aspects of the observed protective effects.

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Vonsenite in Oxide Scales on Iron

INTEREST in the use of inorganic oxide powder coatings to suppress or minimize the oxidation of steel surfaces during high-temperature processes has been growing in recent years^{1–3}. The nature of the powders used and the operative protective mechanisms, however, are complex.

In the course of studying the oxidation process for a simplified system (ortho-boric acid coatings on high purity iron) at temperatures between 700° and 1,100° C in pure oxygen, a complex reaction product in the oxide scale was identified as iron boro-ferrite (4 FeO·Fe₂O₃·B₂O₃), which we believe to be identical to the mineral "vonsenite"⁴. We have not been able to trace any previous published reference to this complex oxide in the oxidation of metals literature. This communication summarizes our preliminary work.

Vonsenite is described⁴ as an opaque mineral, a high-temperature ferrous ferric borate of the ludwigite-vonsenite series, which occurs in skarn in the pyrometasomatic magnetite deposit near New York. The chemical analysis given by Leonard and Vlisidis was: FeO ~54 wt.% : Fe₂O₃ ~30 wt.% :

Silicon Nitride Ceramic Composites with High Toughness

THE brittleness of ceramic materials, compared with metals, limits their use in engineering, in spite of such attractive properties as high temperature strength and oxidation resistance. Possible solutions to the brittleness problem therefore continue to be of interest. One approach advocated¹ for silicon nitride has been that of fibre reinforcement, practical feasibility of which has been demonstrated². In the carbon/silica system Crivelli-Visconti³ and Cooper have shown that high

work of fracture can be obtained: we present here mechanical property data for silicon nitride/silicon carbide fibre composite materials. The potential of silicon nitride ceramics as engineering materials has been described elsewhere⁴.

One advantage is that silicon nitride ceramics made by the reaction of silicon powder with nitrogen undergo virtually no bulk volume change, the 23% lattice volume change being accommodated by growth in inter-particle voids in contrast to the relative fibre/matrix movements in diffusion shrinkage sintering of oxide ceramics. Because the thermal expansion coefficients of silicon and the reinforcing silicon carbide are similar (about $4.5\text{--}5.0 \times 10^{-6}/^\circ\text{C}$), thermal stress mismatch during heating is negligible: on reaction to Si_3N_4 the expansion coefficient of the matrix is approximately halved ($2.8 \times 10^{-6}/^\circ\text{C}$ at $1,000^\circ\text{C}$; $1.6 \times 10^{-6}/^\circ\text{C}$ at 200°C), with the beneficial result that on cooling the SiC reinforcement will be in tension and the silicon nitride matrix in compression, as in pre-stressed concrete. Silicon carbide was chosen for long term compatibility because it is thermodynamically stable with respect to silicon nitride to $1,450^\circ\text{C}$, and, unlike carbon, has oxidation resistance. The thermal programme involved in nitridation somewhat depresses the strength of currently available silicon carbide fibres, and Aveston⁵ has demonstrated strength reductions in certain silicon carbide fibres when they are heated in air and neutral atmospheres. If this strength degradation could be obviated, improved load bearing capacity would result. The thermal conductivity of the reinforcement is much higher than the matrix and is expected to improve resistance to thermal stress.

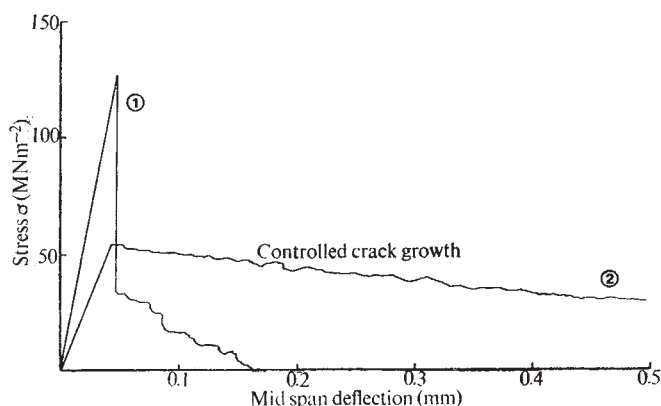


Fig. 1 Stress-strain curves for silicon carbide reinforced silicon nitride exhibiting "tough" fracture behaviour.

We have fabricated $\text{SiC}/\text{Si}_3\text{N}_4$ composites ranging from high density systems fabricated by silicon matrix flame spraying and filament winding to low density matrices made by several methods including slip casting and vibratory compaction. In the results presented here fibres $80\text{--}100\text{ }\mu\text{m}$ diameter consisting of a silicon carbide sheath pyrolytically deposited on a $25\text{ }\mu\text{m}$ tungsten wire (supplied by A. A. Fuller, R. & D. Services) and with typical room temperature properties of $E \sim 420\text{ GN m}^{-2}$ and $\sigma = 1.4\text{--}1.8\text{ GN m}^{-2}$ have been incorporated unidirectionally into low density (about $1.0 \times 10^3\text{ kg m}^{-3}$) silicon powder matrices in volume fractions ranging from $10\text{--}50\%$ and nitrided for various times in the temperature range $1,300^\circ\text{C}$ to $1,450^\circ\text{C}$. The specimens were fabricated by packing a crucible with alternate layers of dry silicon powder and aligned 2 inch lengths of silicon carbide fibre. Specimens $4.5 \times 4.5 \times 51.8\text{ mm}^3$ of reinforced and un-reinforced material made under identical conditions were tested in three point bending at room temperature with a span of 19 mm. Load deflexion traces were recorded and the work of fracture of the reinforced materials determined on un-notched specimens.

Fig. 1, curve 2, illustrates the absence of catastrophic failure of a reinforced silicon nitride, the reinforcement impeding crack propagation and the composite sustaining high percentages of the original load after the onset of matrix cracking. The work of fracture values of such composites with fibre volume fractions ranging from $5\text{--}25\%$ lie in the region $0.2 \times 10^6\text{ ergs cm}^{-2}$ (200 J m^{-2}) to $0.9 \times 10^6\text{ ergs cm}^{-2}$ (900 J m^{-2}): the value 900 J m^{-2} is two to three orders of magnitude higher than the work of fracture for an unreinforced specimen of even higher density. The strength value of 55 MN m^{-2} for curve 2 represents a 60% strength increase compared to an unreinforced specimen of strength 34 MN m^{-2} (density about $1.5 \times 10^3\text{ kg m}^{-3}$).



Fig. 2 Fracture surface of silicon carbide reinforced silicon nitride exhibiting "tough" fracture behaviour; see Fig. 1, curve 2. ($\times 45$.)

Fig. 1, curve 1, refers to a composite where a modest increase in toughness and crack arrest capability occurred, but where interest centred on the increase in strength from 34 MN m^{-2} to 127 MN m^{-2} as a result of fibre reinforcement. The mechanism of the toughening effect demonstrated in Fig. 1, curve 2, is illustrated in Fig. 2, which shows a rough, uneven fracture surface with many fibre pull-outs and suggests additional energy is adsorbed by fracturing the silicon carbide/fibre core interface.

The work of fracture values can be influenced by altering the interfacial adhesion between the SiC fibre and the Si_3N_4 matrix, and between the silicon carbide fibre and its substrate. High bond strengths in general have produced materials of lower toughness whereas low bond strength systems in general produce high toughness values. Low fibre/matrix bond strengths are in general produced with low density matrices and low nitriding temperatures.

The work of fracture values obtained, 900 J m^{-2} , are significant from the engineering point of view; this value is almost as high as that for cast iron. It is now not unreasonable to suppose that with further development such materials as fibre reinforced silicon nitride could well become important tough engineering materials capable of use at higher temperatures than currently available metals.

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Received July 6; revised September 1, 1970.

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Negative Enthalpies of Activation and Proton Tunnelling in Solution

WE have recently made a number of rather precise measurements of the first-order rate constant for the S_N1 solvolysis reaction between benzyl chloride and water, that is



Both the temperature and the pressure coefficients of the rate constant were determined and particular attention was given to the temperature range 0–10° C.

Table 1 First Order Rate Constants for the Hydrolysis of Benzyl Chloride; $k \times 10^6$ s

P/atm	0	$t/^\circ\text{C}$ 5	10	15
1	1.33 ± 0.01	1.25 ± 0.02	1.67 ± 0.01	2.92 ± 0.03
500	1.19 ± 0.02	1.42 ± 0.03	2.05 ± 0.05	3.81 ± 0.00
1,000	1.08 ± 0.06	1.53 ± 0.04	2.47 ± 0.03	4.83 ± 0.03
1,500	0.96 ± 0.05	1.74 ± 0.04	2.91 ± 0.02	5.94 ± 0.10
2,000	0.84 ± 0.08	1.90 ± 0.06	3.39 ± 0.05	6.84 ± 0.02

The relevant rate constants are given in Table 1, and are illustrated in Figs. 1 and 2. It will be evident that at one atmosphere the rate constant as a function of temperature passes through a minimum at or near 4° C and that below this temperature the activation enthalpy for this reaction is negative. It might initially be thought that this surprising fact was the result of an undetected experimental artefact except that it is well outside the experimental error and that, in any case, it is the confirmation of a systematic trend seen in all the other results for this system at other pressures. Perhaps the most conclusive evidence of all that a profound change occurs in the reaction mechanism lies in the independent fact that the volume of activation changes from -4 to $+4$ ml. mol^{-1} over the small temperature interval $+6^\circ\text{C}$ to 0°C . As the normal isobaric enthalpy of activation (and also the corresponding isochoric quantity) decreases to zero and eventually changes sign, the entropy of activation (as evaluated from the transition state theory) decreases rapidly and at the extreme of the measurements reported here reaches -50 calories $\text{deg}^{-1} \text{mol}^{-1}$.

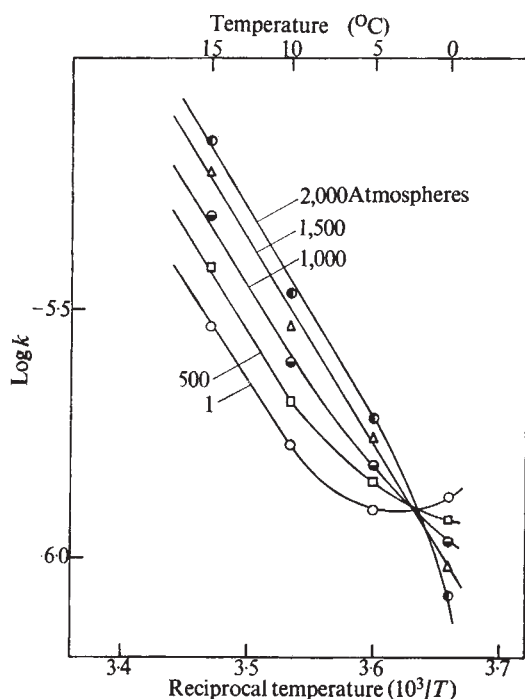


Fig. 1 The first order rate constant as a function of temperature and pressure.

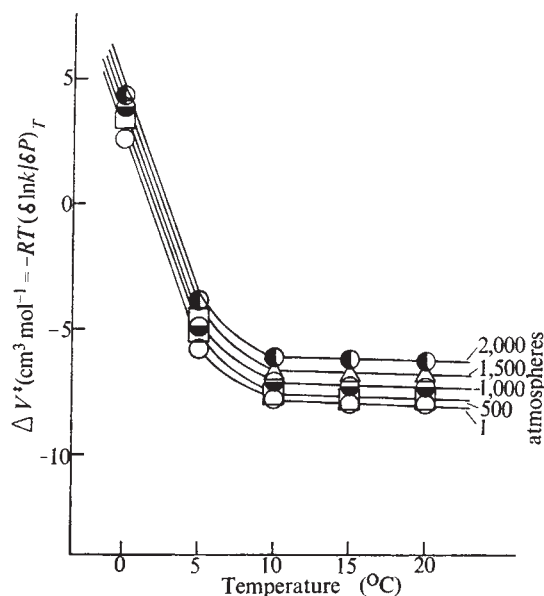


Fig. 2 Volume of activation as a function of temperature and pressure.

All of these data suggest that at temperatures approaching the freezing point of water, this hydrolysis reaction undergoes a marked change in mechanism and in the degree of order associated with the transition state. The high degree of order can only be associated with the solvent and it is reasonable to suppose that the transition state involves a large clathrate structure of water molecules. The apparently athermal isochoric mechanism that ultimately leads to the replacement of the chlorine atom by a hydroxyl group could then be explained in terms of a proton transfer reaction involving firstly the interaction of the benzyl carbonium ion with the lone-pair electrons of the nearest water molecule and secondly the virtual transfer of a proton from this water molecule to the periphery of transition state complex. An alternative way of describing the same process would be to suggest that the frequency of formation of the benzyl carbonium ion is intrinsically high but that fast intermolecular charge transfer and displacement of the proton is only possible given the particular clathrate structure which forms at low temperatures. The word clathrate is used to emphasize that the structure is one imposed by the solvent and, whether or not this structure is one of the recognized modifications of ice, it is clear that its persistence and effectiveness (which may be related to its size) are very sensitive to temperature and also to pressure. Given, however, that the correct local structure is formed in relation to the reacting molecule, then evidently proton transfer from the carbonium ion is fast and the reaction and results presented here are the best evidence obtained so far for tunnelling processes in solution. The question of experimental evidence for tunnelling in solution is discussed in Laidler's recent monograph¹ which draws attention to some earlier work^{2,3} in which distinct curvature from an otherwise linear Arrhenius plot was evident at 20° C. Similar deviations were noted by Caldin *et al.*^{4,5} although at much lower temperatures and in other solvents.

It is interesting to enquire why this additional evidence for the special properties of water has not been detected before. It may of course be a special property of benzyl chloride, but this seems unlikely. (The point is being investigated.) The answer may be that the precision of most measurements of rate constants has been insufficient to establish the relatively small eccentricities in rate constant which lead to these observations. It must also be noted, however, that remarkably few systematic kinetic measurements have been made on aqueous systems at temperatures below 15° C and that many of the

reported values of rate constants at 0° C are the result of (perhaps unwise) extrapolations from higher temperatures.

There is therefore, in our opinion, a need to explore more thoroughly the rates of reactions involving water over smaller intervals of temperature and especially at temperatures lower than 15° C. A fuller description of the present measurements will appear elsewhere.

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BIOLOGICAL SCIENCES

Handedness and Birth Order

IN spite of much speculation on the matter, the aetiology of left-handedness remains elusive. Investigators have considered heredity, neurological pathology, imitation and negative personality, but the evidence in support of any particular hypothesis is inconclusive. There are, however, some suggestive facts. The frequency of left-handedness is greater in males and in twin births, both of which are also associated with greater birth and infant mortality and, in the case of males, a higher rate of spontaneous abortion. The pre-natal and peri-natal periods seem to be more stressful for these groups. Left-handedness is also associated with language disorders such as stuttering, dyslexia, and mental retardation, conditions where central nervous system pathology may be implicated¹. This suggests that the incidence of left-handedness might be correlated with stressful pre-natal and birth conditions. Such difficulties are most characteristic of primiparous births (longer labour and more use of instruments) and births to older mothers. Thus high risk birth orders would be the first born and the late-born (defined here as fourth or later birth).

The relationship between left-handedness and birth order was studied for a sample of ninety-five left-handed university students, fifty-four male and forty-one female. Handedness was classified by asking each subject, "Which hand do you usually use for writing?". Previous work has shown that the reply (right or left) is as good a behavioural criterion as any other. A group of 553 right-handed students (262 male and 291 female) served as a control group.

Table 1 Handedness and Birth Order

Birth order	All Ss		Group male handedness		Female	
	R	L	R	L	R	L
1, 4+ (high risk)	250	56	117	34	133	22
2, 3 (low risk)	303	39	145	20	158	19
	$\chi^2=6.16$		$\chi^2=5.71$		$\chi^2=0.91$	
	$P=0.02$		$P=0.02$		$P=0.50$	

Table 1 shows the relationship between handedness and the two categories of birth order, high risk (first birth or fourth and later births) and low risk (second and third births). For the group as a whole (male and female) there are more left-

handed people in the high risk birth order category. The chi-square value, based on analysis of a 2 × 2 contingency table, birth order and handedness, is 6.16 (d.f.=1, $P<0.02$). The fifty-six left-handed cases in the high risk group are thus significantly more than the forty-five cases that would be expected by chance. For the incidence of left-handedness in high-risk male subjects alone, $P<0.02$ (chi-square=5.71, d.f.=1). For the female subjects alone, there is a nonsignificant trend in the same direction.

These results support the hypothesis that there is a relationship between handedness and birth order, which suggests a relationship between left-handedness and neurological insult associated with pre-natal or delivery factors.

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Patterned Response to Song in Cricket Central Auditory Neurone

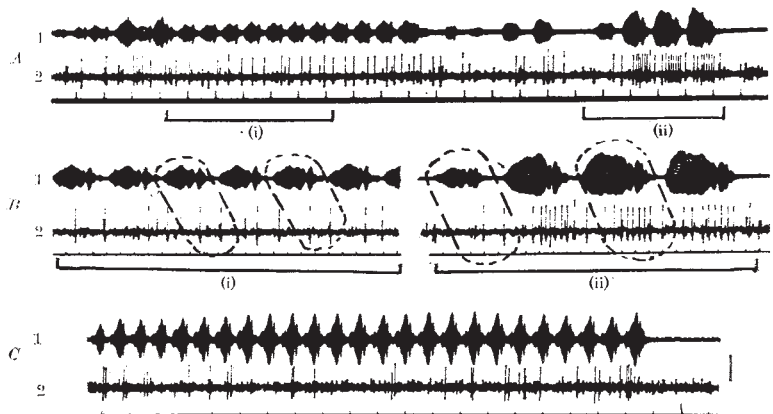
THE acoustic behaviour of many Orthopterans is familiar and well documented¹. The evidence suggests that females are phonotactic to the calling song of the conspecific male², that phonotaxis occurs with greater probability when the calling song is that of a conspecific rather than a heterospecific male³, that males as well as females exhibit phonotaxis⁴ and that males respond to each others' song by stridulating in turn⁵ and by synchronizing their chirps⁶.

In order to find sensory neurophysiological correlates of acoustic behaviour, the activity of central auditory neurones in the neck connectives of several species of crickets has been recorded. One central auditory neurone of an East African field cricket tentatively identified as a *Liogryllus* sp. responds to recorded song with trains of action potentials which conform to the temporal pattern and the intensity of the song (Fig. 1A and B). For the purpose of brevity, this neurone will be called the ϕ neurone.

The ϕ neurone is the first unit recorded from an Orthopteran to be shown to have the properties of a song-responding unit. A number of other central auditory neurones have been characterized in Gryllid, Acridid and Tettigonid nervous systems, but most are highly phasic and/or rapidly habituating units of large diameter which seem to be suited for warning functions; they lack the proper qualifications for a song-responding fibre: the T fibre of the Tettigonid *Homorocoryphus* is inhibited by song and another smaller central fibre of this animal responds to song with no regular pattern⁷. The T fibre of *Gampsocleis buergeri*, another Tettigonid, shows habituation in response to its species song⁸. Several central auditory neurones of other cricket species and other central fibres of *Liogryllus* sp. have been tested and do not show patterned response to song (M. D. Z., in preparation) (Fig. 1C).

The ϕ neurone responds to song with a train of action potentials for each sound pulse of the song (Fig. 1A, B). The number of action potentials in each train is proportional to the logarithm of the energy of each sound pulse which is given approximately by the product of the maximum intensity and the duration of the pulse (Fig. 2). The first action potential of each train is delayed by 15–20 ms from the start of the sound pulse, the delay varying inversely with the initial rate of increase of the sound intensity. The last action potential occurs with a

Fig. 1 Activity of two central auditory neurones of *Liogryllus* sp. in response to cricket song. *A*, Response of the ϕ neurone; *B*, response of the ϕ neurone on an expanded time scale. Intervals (i) and (ii) correspond to the respective bracketed intervals of *A*. The dashed curves enclose a sound pulse of the calling song and the corresponding ϕ neurone response. *C*, Response of another central auditory neurone which does not follow the song pattern. Trace 1, the cricket song as monitored by a Brüel and Kjøer 1/4 inch condenser microphone. Trace 2, the activity of the central auditory fibre recorded extracellularly from the neck connective. Time marker: *A* and *C*, 50 ms; *B*, 10 ms. Vertical scale; *A*, *B* and *C* = 100 μ V.



delay of 10–15 ms after the end of the sound pulse. The interval between the onset of successive pulses of a trill is approximately 50 ms with a 5–10 ms interpulse interval. Each train of unit responses to a single sound pulse is thus well separated from the train of responses to the next pulse (Fig. 1 *A*, *B*).

The response of the ϕ neurone to artificial pulses of pure tones varies little over the range of frequencies between 5 and 50 kHz. The response falls off both above and below this range. There is no response at all when the tympanal organs are removed. In the absence of transients, artificial sound pulses of pure frequencies less than 5 kHz produce less of a response in the ϕ neurone than do those of pure frequencies greater than 5 kHz. When transients are introduced into these lower frequency artificial sound pulses, however, the ϕ neurone responds as well as it does at higher frequencies. These results correlate with behavioural responses to artificial sound pulses in three species of Acrididae of the genus *Chorthippus*, which respond phonotactically to artificial sound pulses with greater probability when transients are present than when they are absent^{9,10}.

Unlike other Orthopteran central auditory neurones which have been tested (refs. 7 and 10, and M. D. Z., in preparation), the ϕ neurone shows little or no response decrement during prolonged stimulation, such as 2 min of song or artificial pulse trains with pulse intervals of 1 s or less. There are obvious advantages to having a non-habituating neurone for listening to the song of another animal: Orthopterans will sing for hours at a time; orientation and phonotaxis involve continuous

listening for minutes at a time, and alternate singing between males can go on for 2 h (ref. 5).

The response of the ϕ neurone to song invites comparison with the response of the A fibres of the tympanic nerve of certain families of moths to the cries of hunting bats¹². Both fibres code for certain features of their respective stimuli: pulse intensity, pulse duration, interpulse interval and the duration of the pulse train. Both fibres are insensitive to frequency within a broad range.

Further observations on the response of the ϕ neurone and possibly other song-responding neurones to songs of hetero-specific animals and to the different songs of the adult repertoire of conspecific animals could contribute to a better understanding of the sophisticated neurophysiological mechanism by which Orthopterans distinguish between song patterns.

I thank Dr C. H. Fraser Rowell for his sponsorship and encouraging criticism, and Dr Rowell, Dr D. R. Bentley, Dr R. R. Hoy and Kathleen M. Zaretsky for discussions and criticism of the manuscript.

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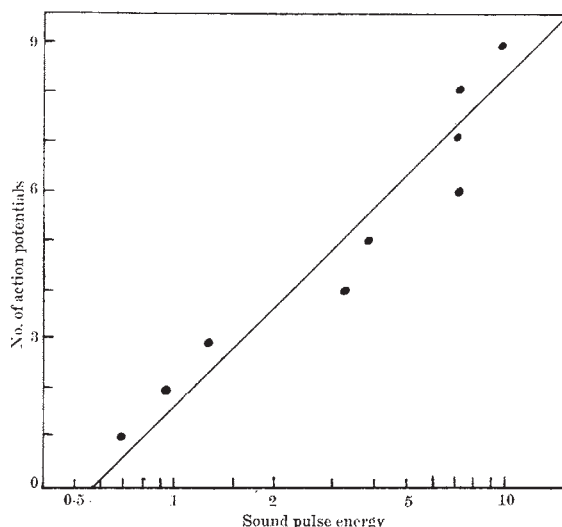


Fig. 2 Number of action potentials of the neurone in response to individual sound pulses of the species calling song plotted as a function of the energy of each pulse (●). Energy is plotted on a logarithmic scale in dimensionless units. The values of energy are relative. The straight line was obtained by a least squares regression from the data points shown.

Trial with a Transponding Acoustic Fish Tag tracked with an Electronic Sector Scanning Sonar

A TRANSPONDING acoustic fish tag has been developed for use with the ARL scanner which is fitted to the Ministry of Agriculture's research vessel Clione. The design and installation of the ARL scanner have been described already^{1,2}. The sonar transmitter floodlights a volume of sea, 30° in one plane by 10° in the other, by transmitting an acoustic pulse which lasts 100 μ s, two or four times per second. This gives a range resolution of 7.5 cm and maximum ranges of 366 m and 183 m respectively. A receiving beam is swept over the same volume 10,000 times per second, with a resolution of 0.33°

in the 30° plane. Thus, with this beam sweeping in the horizontal plane, a plan position display (CRT) is obtained of targets in midwater or of features on the seabed. The mode of operation can be changed so that the beam scans in the vertical instead of the horizontal plane. In this case the depth of a target can be obtained as well as a profile of the seabed.

Although shoals and individual fish have been tracked in favourable circumstances by their echoes on the display³, it became clear that a positive means of identifying and tracking was needed⁴. This need has been met by a transponding system which is attached to the fish; it consists of a receiver and transmitter working at 300 kHz, which is the carrier frequency of the ARL scanner. The signal received from the sector scanner is amplified and used to trigger a transmitter which forms part of the tag. A pulse, lasting 3 ms, is returned to the sector scanner where it appears as a bright rectangle on the display. (A detailed description of the tag will be published elsewhere.)

An acoustic tag was attached to the dorsal side of a 43 cm plaice (*Pleuronectes platessa* L.) by means of a short length of monofilament nylon tied to a conventional Petersen tag; the fish was then tracked in the Shipwash-Inner Gabbard area of the southern North Sea, which has a uniform depth of approximately 27 m and a bottom consisting of sand and gravel. The fish, released at 1000 h on July 8, was followed for 15 h; tracking ceased because of operator fatigue. Contact was maintained up to distances of 365 m, but a range of 140–230 m was found to be most suitable for ship handling. The position of the fish relative to the ship was logged by recording ship's head, ship's position from the Decca Navigator, and the range and bearing of the fish from the ship. The maximum error of the Decca system varied from ± 23 m in full daylight to ± 46 m at night (Decca Navigator sheet 3A). In this manner the fish's track was built up from a succession of fixes. When contact was lost it could be regained by steaming along a grid covering the fish's predicted position. This information was supplemented by photographic (16 mm film) and videotape recordings of the display.

The signal received on the ARL scanner is shown in vertical mode in Fig. 1. The course followed by the fish (Fig. 2) followed the tidal cycle (on the surface). The results are given in Table 1.

Tidal information (direction 030° NE, speed 2 kn, and 206° SW, 2 kn) was taken from an Admiralty chart and tables⁵.

The fish seemed to spend about 70% of the time off the

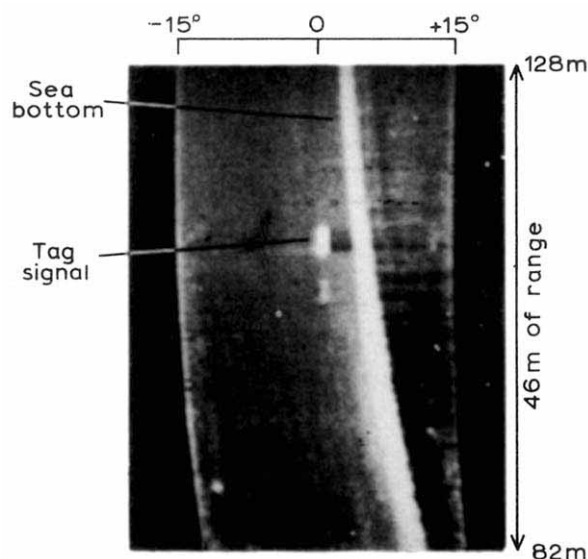


Fig. 1 The transponding tag signal shown at 110 m range in vertical mode on the ARL scanner. Tilt angle was 8°, and the plaice was 4 m above the sea bottom. The bearing relative to the ship was starboard 35°.

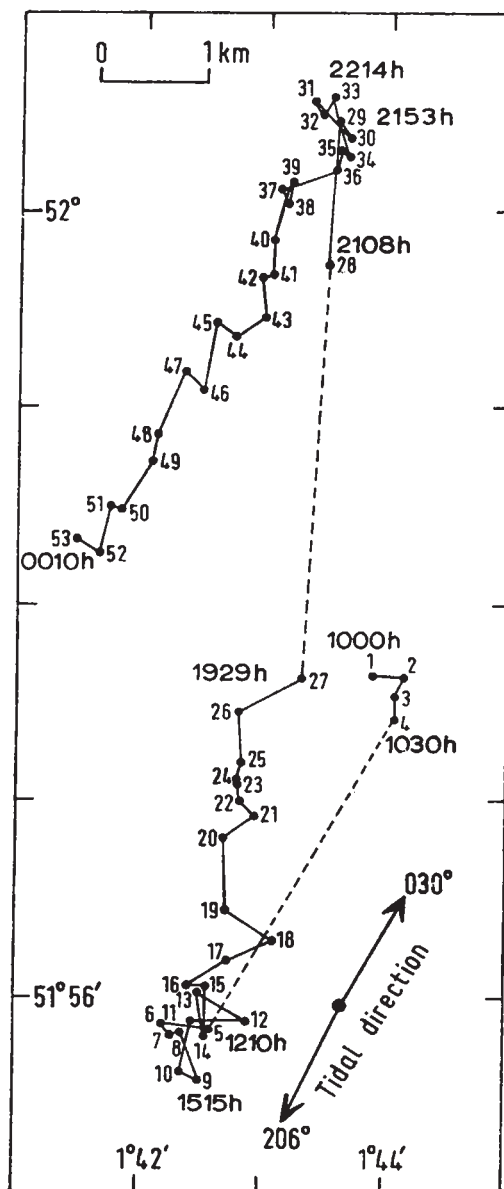


Fig. 2 The course followed by the tagged plaice after release at station 1. The numbers represent consecutive position fixes and the broken line shows where contact was lost.

sea bottom; at night its average height off the bottom increased from 2 m to 6.7 m, which is in agreement with the results of laboratory experiments on plaice⁶. When the fish was on the bottom the signal was not always easily recognizable, possibly because the animal was burying itself in the sand and gravel.

Table 1 Tracking the Fish

Time (BST)	Station	Remarks	Tide	Distance moved (km)	Speed (fish length/s)
1000–1515	1–9	In contact	206°	5.19	0.64
1030–1210	4–5	Lost contact			
1515	9		Slack water		
1515–2153	9–29	In contact	030°	12.04	1.17
1929–2108	27–28	Lost contact			
2153	29		Slack water		
2153–0010	29–53	In contact	206°	7.41	14.6

Although there have been previous tracking records⁷⁻⁹ the technique described here gives detailed information about depth, position and the relation of fish to bottom features; it has applications to the study of fish behaviour and migration and the reaction of fish to gear.

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Received August 14; revised October 28, 1970.

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Measurement of Antitumour Activity of Actinomycin D

SEVERAL antibiotics are being used as antitumour agents because of their cytotoxic activity against both proliferating and non-proliferating cells¹ but the doses of the substances given to patients are largely judged by empirical observations. Clearly it would be more satisfactory if the antitumour activity could be measured in the laboratory. It has already been

reported² that HeLa cells, normally unable to grow in the mouse, will develop into a rapidly growing tumour if the immune mechanism of the mouse has been suppressed by antilymphocyte serum (ALS). Such an animal may be most useful for measuring the antitumour activity of drugs and the purpose of this report is to describe our early findings.

Antilymphocyte serum was prepared by the method of Levey and Medawar³ and the *in vivo* activity measured as described by Stanbridge and Perkins². Groups of 10 CBA mice were given ALS (0.25 ml.) on days -1, 0, 1, 3, 9 and 16 to suppress the immune response and HeLa cells (0.2 ml. containing 2 to 4 × 10⁵ cells) were injected by the subcutaneous route in the lower ventral region. Actinomycin D (Calbiochem Ltd) was also given subcutaneously at the time and dosage indicated (Tables 1 and 2) into the site of injection of the HeLa cells. In all experiments control groups of mice were included; the one had ALS and HeLa cells whereas the other had HeLa cells alone.

In the first experiment the effect of giving a fixed dose (6 µg) of actinomycin D at different times (0, 2, 6 or 10 days) after giving the HeLa cells was studied (Table 1). In normal mice the HeLa cells remained localized at the site of injection and established small tumours that could be palpated by day 4. The rate of regression, however, was always rapid and by day 12 all the tumours had gone. In ALS treated mice the established tumours rapidly progressed and it was common to find that by day 10, when the tumours in all normal mice had regressed, they had grown to more than 1 cm in diameter.

Giving 6 µg of actinomycin D into the same site at the time of giving the HeLa cells brought about total regression of the tumours in all mice by day 16. Delay in giving the same dose of actinomycin D, however, caused the tumours to regress more slowly, possibly because of the greater number of cells involved, but eventually all were regressed.

The dose required for antitumour activity was studied by giving the drug (2 µg, 4 µg or 6 µg) either at the same time as giving the HeLa cells or 2 days later and the results are shown in Table 2. Although 2 µg given on day 0 was more effective than the same dose given on day 2, the overall antitumour activity was slight which indicates that this may be the lowest effective dose for the number of HeLa cells given. On the

Table 1 Antitumour Activity of Actinomycin D given at Various Times after HeLa Cells

Percentage of mice with tumours on day :											
Actinomycin D (6 µg) given on day :	4	6	10	15	20	23	26	29	33	37	40
0	100	100	60	40	0	0	0	0	0	0	0
2		100	50	30	10	0	0	0	0	0	0
6		100	100	100	60	40	30	20	0	0	0
10			90	90	80	70	30	10	0	0	0
Controls											
ALS and HeLa cells without actinomycin	100	100	80	80	80	80	60	60	40	30	30
HeLa cells alone	100	90	40	0	0	0	0	0	0	0	0

Table 2 Antitumour Activity of Various Doses of Actinomycin D given on Day 0 or 2 after HeLa Cells

		Percentage of mice with tumours on day :														
Actinomycin (µg)	Given on day	6	10	13	15	17	21	23	27	30	34	43	49	51	55	
2	0	30	10	10	10	10	10	20	30	30	20	0	0	0	0	
4	0	70	20	10	0	0	0	0	0	0	0	0	0	0	0	
6	0	70	20	10	10	0	0	0	0	0	0	0	0	0	0	
2	2	60	40	20	60	70	70	70	60	50	40	10	0	0	0	
4	2	80	30	30	30	30	30	40	50	50	40	20	10	10	0	
6	2	90	70	40	40	30	30	30	50	40	20	10	0	0	0	
Controls : ALS and HeLa cells without actinomycin		90	100	100	100	100	100	100	90	90	60	60	20	20	20	

other hand both 4 μ g and 6 μ g caused total regression when given on day 0 but the effect was reduced when the injection was delayed until day 2.

The antitumour activity of other antibiotics is now being studied using this test system.

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Received May 22, 1970.

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New Model for Schistosome Granuloma Formation using a Soluble Egg Antigen and Bentonite Particles

INJECTION of purified *Schistosoma mansoni* eggs into mice results in granuloma formation¹, and it has been shown that egg antigen is gradually released to phagocytes which accumulate around the eggs and engage in antigen sequestration and destruction *in situ*². Schistosome granuloma formation as seen in the infected host is a complex immunological response probably involving several synergistic mechanisms³. In experimental anamnestic granulomas of mice, the augmented and accelerated cell response is mediated by delayed hypersensitivity⁴ and is partly suppressed by immunosuppressive drugs, neonatal thymectomy, ALS (antilymphocyte serum) and X-irradiation⁵⁻⁸; it is slightly inhibited by ellagic acid⁹. Soluble egg antigens have been obtained from schistosome eggs by phosphate buffered saline (PBS) extraction and ultracentrifugation which enhance granuloma formation around schistosome eggs in mice and induce dermal reactivity in the mouse footpad (unpublished work of D. L. Boros and K. S. Warren). This material is currently being analysed immunochemically.

In communication with but independently from the authors of the preceding communication¹⁰, we have assayed a new experimental granuloma model which involves the adsorption of known amounts of antigens or of irritative metabolites onto bentonite carrier particles, followed by quantitative study of the host tissue responses.

An extract of *S. mansoni* eggs, prepared by grinding 50,000 purified eggs/ml. in PBS¹² at 0° C and removing the solids by centrifugation at 100,000g, was supplied by Warren and Boros. Between 12,000 and 36,000 Indian Head Bentonite (Johns Manville Co., Chicago, Illinois) particles, up to 60 nm across, obtained by sieving, were suspended in 1 ml. of the antigen, shell-frozen and the water removed by lyophilization. Particles coated with soluble egg antigens were resuspended in 2.5 ml. PBS and 0.2 ml. per animal was introduced through a paediatric scalp vein set through the tail vein into the pulmonary microvasculature of sensitized and unsensitized white Swiss mice. Uncoated bentonite particles similarly suspended and injected served as controls. Mice were sensitized by injecting intraperitoneally 0.1 ml. of a 1:5 PBS dilution of soluble egg antigens, 1 week before injection of particles. After 2 days, mice were killed by cervical fracture and the lungs were fixed *in situ* by tracheal injection of buffered formalin. After embedding in paraffin, lungs were sectioned in 6 nm slices and stained with haematoxylin-eosin².

For measurement with the ocular micrometer, granulomas were treated as ellipsoids. Two values in micrometer units

were obtained by measuring the extent of the granuloma along the major axis *A, A'* and a minor axis *B, B'* and bentonite particle length was subtracted from *A, A'* and width from *B, B'*. The sizes of granulomas were determined by taking the mean value for ten granulomas per mouse. The group mean was calculated by averaging mean values up to 100 mice. The significance of data was determined by Tukey's test¹².

Uncoated bentonite produces a minimal response to foreign body cells which is not affected by host sensitization. Coating with soluble egg antigens does not change this response in the unsensitized mouse, but in the sensitized animal a florid granulomatous cell response occurs on the second day. Preliminary observations of similar animals on the eighth day after injection have shown that the cell response declines in all experimental groups. Anamnestic response to soluble egg antigen results in granuloma formation in the sensitized animals, although no haemagglutinating antibody to soluble egg antigens can be demonstrated in the mice during the first 2 weeks after intraperitoneal sensitization (unpublished work of Boros and Warren).

Table 1 Comparison of Granuloma Sizes 2 Days After Injection of Particles

Condition of mouse	Type of particle	Size of granuloma (μ m $\pm$ s.e.)	No. of mice	Significance (%)
Unsensitized	Uncoated	32.1 $\pm$ 1.3	5	—
Sensitized	bentonite	14.3 $\pm$ 2.0	3	—
Unsensitized	Antigen-coated	26.7 $\pm$ 1.4	7	—
Sensitized	bentonite	98.9 $\pm$ 10.4	10	0.1

In contrast with previous studies with whole schistosome eggs¹⁻⁸, peak cell reaction to soluble egg antigens in this model occurs by the second to fourth day and includes numerous polymorphonuclear leucocytes, some macrophages and eosinophils and fibrin. In preliminary observations, we have confirmed the persistence of experimental granulomas until the eighth¹⁰ and sixteenth days, with a change in cell population at the later stages¹⁰. It is not known whether natural soluble egg antigens are mixed or conjugated with other egg metabolites, but their mode and speed of release in the bentonite model can be assumed to differ from those in the intact ovum.

We are now completing studies on the effect of lysophosphatides using a similar experimental model. Lysophosphatides have been identified in *S. mansoni* eggs by thin-layer chromatography and, histochemically, lecithins and cephalins were found to be concentrated in the apical glands of mature miracidia and in their ducts¹³. Protein is also present, and it has been shown that miracidial homogenates and hatching fluid are capable of sensitizing mice for accelerated granuloma formation¹⁰; thus, further studies of the components of apical gland secretion and on their biological effects may be useful for understanding the pathogenesis of bilharzial disease. Our model should also be applicable for studying other problems of granulomatous inflammation.

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Specific Granulomatous Hypersensitivity elicited by Bentonite Particles coated with Soluble Antigens from Schistosome Eggs and Tubercle Bacilli

THE infectious granuloma is a form of focal inflammation which occurs around various infectious agents¹. The schistosome egg granuloma has been investigated as a model of granulomatous inflammation², and it has been shown that mice previously exposed to eggs of *Schistosoma mansoni* develop larger granulomas than unsensitized mice and that peak size is attained earlier³. The anamnestic response is specific, it can be transferred passively with lymphoid cells, but not by serum, and is inhibited by immunosuppressive drugs⁴, neonatal thymectomy⁵ and anti-lymphocyte serum⁶. It has been concluded therefore that the formation of granuloma around *S. mansoni* eggs is a manifestation of delayed hypersensitivity.

Soluble egg antigens isolated from homogenized schistosome eggs⁷ can both induce delayed hypersensitivity granuloma formation and elicit dermal reactivity in mice (our unpublished work). This provided an opportunity to investigate the function of these antigens in the elicitation of the granulomatous response, using bentonite particles the size of the schistosome egg as a nidus around which granulomas could form in the lung. Repeated experiments with such particles, onto which the soluble egg antigens have been adsorbed, brought about a granulomatous response in sensitized hosts which resembled in size and cellularity the schistosome egg granuloma. By the same technique, two other antigens were used for the purpose of comparison: (1) a filtrate of *Mycobacterium tuberculosis*, and (2) bovine serum albumin.

Female mice (CF 1 strain) weighing 18–22 g were sensitized by an intraperitoneal injection of either 1,000 viable schistosome eggs in 0.5 ml. saline, or soluble egg antigens (SEA)⁷ in a concentration equivalent to 1,000 eggs containing 8–10 µg of protein as measured by the method of Lowry⁸. Another group of similar animals was injected subcutaneously with 0.2 ml. of a mixture of equal volumes of a ten-fold concentrated culture filtrate (MCF) of *Mycobacterium tuberculosis* strain H₃₇Ra (ref. 9) and Freund's complete adjuvant ('Difco') containing the same strain of mycobacteria. A third group was injected intraperitoneally with 500 µg of crystalline bovine serum albumin (BSA) (Pentex, Kankakee, Illinois) in 0.5 ml. of saline. Ten days later, sensitized mice and unsensitized controls were challenged with bentonite particles to which the different antigens (SEA, MCF, or BSA) were adsorbed.

Indian Head bentonite (325 mesh) (Johns Nanville Products Corporation) was washed several times in saline and was then sieved through filters until particles were 70 ± 4 µm (as measured *in vitro*). Twenty thousand particles were suspended in 1 ml. of the following antigen solutions: (1) SEA containing 0.6 mg protein, (2) MCF containing 5 mg protein and (3) BSA con-

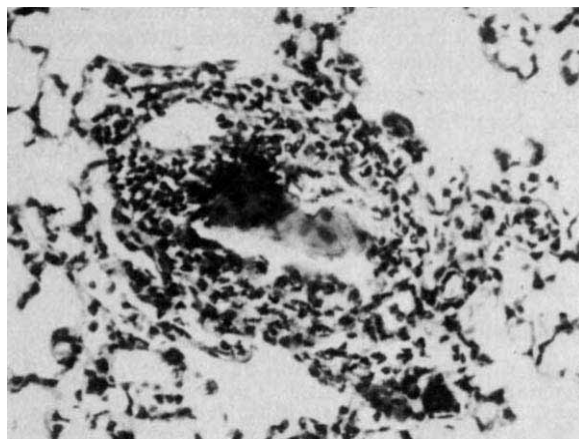


Fig. 1 Granuloma formation after 4 days around SEA-coated bentonite particle in the lung of mouse sensitized with schistosome eggs. (Stained with haematoxylin and eosin × 250.)

taining 10 mg of protein. Particles were incubated for 30 min at 15° C, washed twice in phosphate buffered saline, pH 7.2, and resuspended in 0.9% saline to a concentration of 6,000 particles/ml.; 3,000 particles in 0.5 ml. were injected by way of the tail vein into the pulmonary microvasculature of groups of mice. Eight days later mice were exsanguinated and their lungs were filled with buffered formalin, removed and sectioned. Sections, 5 µm thick, were stained with haematoxylin and eosin. The size of the granulomas was determined by measuring two diameters at right angles to each other with a Cooke AEI image splitting eyepiece. Mean diameters of lesions were calculated for each group. Significance was evaluated by Student's *t* test. The results are shown in Table 1.

Table 1 Granuloma Formation After 8 Days Around Bentonite Particles With or Without Adsorbed Antigens Injected Intravenously into Lungs of Unsensitized and Sensitized Mice

Sensitization	Particles injected			
	Bentonite alone	Bentonite with SEA	Bentonite with MCF	Bentonite with BSA
	Mean granuloma diameter µ ± s.e.			
Unsensitized	54.78 ± 1.72 6/66§	77.61 ± 2.14* 6/84	58.15 ± 3.32† 6/91	52.32 ± 1.68‡ 6/75
Sensitized with eggs	63.97 ± 1.77 6/97	110.40 ± 3.24* 6/110	66.29 ± 2.97 6/145	65.47 ± 2.81 6/60
Sensitized with SEA	54.86 ± 2.99 3/34	93.71 ± 3.71* 6/64		55.62 ± 2.31 3/35
Sensitized with MCF		74.23 ± 3.60 6/100	82.86 ± 4.39† 6/100	
Sensitized with BSA				58.29 ± 3.52‡ 6/59

* Significance < 0.0005 highly significant.

† Significance < 0.005 highly significant.

‡ Significance < 0.05 not significant.

§ No. of mice/No. of lesions read.

Bentonite particles alone, regardless of the immune state of the animals, evoked a minor cellular reaction composed chiefly of macrophages as seen in a foreign body granuloma. Mean diameters of uncoated particles measured in the tissues only rarely reached the 70 µm measured *in vitro*. Because particles lie at different angles in the tissues, sectioning cannot always cut through their maximal diameter. The same type of granuloma was produced when particles coated with SEA, MCF or BSA were injected into unsensitized mice, but the SEA-coated particles evoked a somewhat larger reaction (Table 1). This may have been caused by some nonspecific component¹⁰ of the relatively crude antigenic mixture.

In contrast, injection of particles coated with SEA or MCF antigens into specifically sensitized mice evoked large granulomatous lesions which contained not only macrophages but numerous eosinophils and occasional giant cells. Lesions in specifically sensitized mice were significantly larger ($P \leq 0.005$) than in unsensitized mice (Table 1). Furthermore, no cross-reactivity could be seen among the different antigen-coated particles. Finally, injection of bentonite particles coated with an unrelated soluble antigen, BSA, did not evoke an anamnestic, augmented granulomatous response. This may indicate that these artificial granulomas can be produced only in systems of delayed hypersensitivity.

Granulomas around schistosome eggs in sensitized mice reach their peak 8 days after injection. For comparison, bentonite granulomas were measured at the same interval, but this timing proved sub-optimal. Information received from F. von Lichtenberg *et al.*¹¹ suggests that they have found maximal cellular reactions around bentonite 2–4 days after injection, and we confirmed this observation by carrying out an additional experiment in egg-sensitized mice. Considerably larger granulomas were measured after 4 days than after 8 days (Fig. 1). For example, granulomas around uncoated bentonite particles which measured $63.97 \pm 1.77 \mu\text{m}$ after 8 days in the initial experiment were $78.80 \pm 4.6 \mu\text{m}$ after 4 days; SEA-coated particles which had been $110.40 \pm 3.24 \mu\text{m}$ after 8 days were $132.21 \pm 5.5 \mu\text{m}$ after 4 days. The earlier appearance of peak cellular reactions around the bentonite particles may suggest a more rapid release of antigen than from the schistosome egg.

Though our results and those of von Lichtenberg *et al.*¹¹ are not mutually comparable because of differences in the timing of granuloma measurements and in the computing of granuloma diameters, both results show that specifically sensitized mice produce an augmented granulomatous response around antigen-coated bentonite particles.

In summary, a new technique has been developed for the study of granulomatous hypersensitivity, using bentonite particles coated with soluble antigens obtained from schistosome eggs and a *Mycobacterium*. These same antigens may function in granuloma formation during an infection caused by live agents. The evolution of the granulomatous lesion is apparently specific, and the system is applicable to other models. This technique may enable us to evaluate the role of specific antigens in the elicitation of granulomatous hypersensitivity induced by infectious agents.

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Anaemia in Bursectomized Irradiated Chickens

We have found that a significant percentage of bursectomized irradiated chickens develop a severe anaemia. White leghorn chickens (DeKalb strain 161) were surgically bursectomized when they hatched and given 600 r. of X-irradiation as previously described¹. Control animals received X-irradiation only. The animals were housed in conventional animal quarters and given free access to water and food. At 8 weeks of age heparinized blood samples were collected from a wing vein, and red and white blood cells were counted using the Natt-Herrick stain². Blood smears were prepared and stained with Wright-Giemsa stain, and were examined for the presence of immature erythrocyte forms. Further, the number of lymphocytes per microscopic high power visual field was determined. The haemoglobin concentrations and the haematocrits of the blood samples were determined. The Coombs direct test¹⁰ was performed on the blood samples, using a rabbit antiserum raised against chicken IgG as antiglobulin reagent.

The animals were then weighed and killed by cervical dislocation. Smears were prepared from the femoral bone marrow and stained with Wright-Giemsa stain, and the proportion of mature and immature erythrocytes (erythroblasts and polychromatic erythrocytes) was estimated. No significant differences between the mean body weights of the bursectomized irradiated and control chickens were noted (616 ± 35 and 693 ± 24 g respectively).

The haematocrit, the haemoglobin concentration and the erythrocyte count were all significantly depressed in the bursectomized irradiated chickens (Table 1). The mean corpuscular volume and mean corpuscular haemoglobin were not significantly altered in the bursectomized irradiated chickens. The mean corpuscular haemoglobin concentration, however, was significantly decreased. The white blood cell count was significantly lower in bursectomized irradiated chickens. The stain does not accurately differentiate the avian

Table 1 Summary of the Haematological Findings in Control Irradiated (Cx) and Bursectomized Irradiated (Bx) Chickens

Group	No. of animals	Haematocrit (%)	Haemoglobin (g%)	Erythrocyte count (per $\text{mm}^3 \times 10^{-3}$)	MCV (μm^3)	MCH (pg)	MCHC (%)	White blood cell count (per mm^3)	Lymphocytes per visual field*	Mature bone marrow erythrocytes (%)*
Cx	17	28.9 ± 0.9	8.3 ± 0.1	1,822 ± 90	163.5 ± 8.7	0.47 ± 0.02	28.98 ± 0.61	10,194 ± 804	1.42 ± 0.16 (8)	74.7 ± 3.5 (8)
Bx	17	18.8 ± 1.8	4.9 ± 0.6	1,051 ± 144	207.5 ± 20.7	0.51 ± 0.05	25.36 ± 1.12	5,729 ± 626	0.89 ± 0.10 (15)	20.4 ± 7.3 (9)
Comparison Cx-Bx										
t-test (P)		<0.001	<0.001	<0.001	>0.05	>0.05	<0.025	<0.001	<0.025	<0.001

*Figures within parentheses represent the number of animals assayed.

thrombocytes and lymphocytes. The counts on Wright-Giemsa stained smears, however, indicate that the number of lymphocytes (small and medium sized) was significantly decreased after bursectomy. The blood smears of ten out of twelve anaemic bursectomized irradiated, but no control, chickens contained immature erythrocyte forms (range 7–51%, mean 22%). None of the blood sample chickens were Coombs positive.

Examination of bone marrow smears showed that the bursectomized irradiated chickens all had cell rich bone marrow. These chickens also had significantly fewer mature erythrocytes. In bursectomized irradiated chickens with significant anaemia (five out of nine) the mean percentage mature forms was $2.34 \pm 0.96\%$ and in bursectomized irradiated chickens with no significant anaemia it was $42.93 \pm 3.49\%$. In both cases this was significantly lower ($P < 0.001$) than the mean value $74.66 \pm 3.54\%$ of control chickens.

One possible cause of the anaemia is viral or bacterial infections facilitated by the well documented immune deficiency of the bursectomized irradiated chickens³. An autoimmune basis cannot be excluded, although the existing immune deficiency and our failure to demonstrate positive Coombs direct reactions argue against this possibility. Another possibility is a direct involvement of the bursa of Fabricius, by means of cells and/or humoral factors in erythropoiesis. The thymus, another central lymphoid organ, has been implicated in the regulation of erythropoiesis in mice^{4,5}, man^{6,7}, opossum⁸ and rabbit⁹.

This work was supported by grants from the US Public Health Service.

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Received August 11, 1970.

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Content of ATP and ADP in Rabbit Blastocysts

INTEREST in the physiology and biochemistry of the early mammalian embryo has prompted us to make an exploratory study of the content of adenosine triphosphate (ATP) and adenosine diphosphate (ADP) in rabbit blastocysts aged 5–6.5 days. This is a period of rapid growth during which the blastocysts lie free in the uterine horns, until antimesometrial attachment takes place on day 7 of gestation (the day of mating being referred to as day 0).

Blastocysts were recovered from untreated or treated Nembutalized rabbits with the minimum of delay, directly from the

exposed surface of the endometrium. To prevent loss of ATP by time-consuming handling, numbers but not weights of embryos were recorded. Three methods of extraction were examined and found to yield satisfactorily reproducible results: (1) blastocysts were placed in a small volume of ice-cold trichloroacetic acid 20% (TCA) or (2) they were frozen in solid CO₂ and subsequently thawed in 20% TCA; to facilitate penetration of acid the blastocysts were punctured after thawing with a steel needle; (3) the blastocysts were immersed in methanol as described in the method for the fixation and preparation of rabbit flat-mounts¹ and left for 10–15 min with two changes of methanol (to compensate for dilution of methanol with blastocyst fluid); blastocysts were then punctured, excess of methanol drained and the tissue frozen in solid CO₂ before extraction with TCA. The samples containing blastocysts (three to sixteen in our experiments) were next centrifuged, neutralized and the volume made up to 2 ml.; depending on the number of embryos extracted, 10 µl. or 100 µl. aliquots were used for the measurement of ATP and ADP by the firefly luciferase system².

At the developmental stage chosen for our experiments, during which the average fresh weight of a rabbit blastocyst increases from 1 mg at 5 days to 100 mg on day 6, the content of ATP and ADP per blastocyst also increases considerably (Table 1). The blastocysts seem to be in a logarithmic phase of growth at this stage. A linear regression was fitted for the log₁₀ (ATP+ADP) content against age for the fifteen samples of untreated blastocysts. The fitted line has a correlation coefficient of 0.95 and indicates that the content of (ATP+ADP) doubles every 9 h. The ratio of ATP to ADP is similar to that found in other mammalian tissues^{3,4}. The variability in nucleotide content encountered in different batches of coaeval blastocysts is in keeping with morphological observations as well as data obtained for other chemical constituents of rabbit blastocysts^{5,6}, all of which indicate marked differences in blastocysts within and between litters.

When rabbit blastocysts are left for 1 or 2 h at 37° C, in excised unopened uterine horns, increasingly anoxic conditions develop around the embryos, causing extensive cellular disorganization throughout the blastocyst⁷. Table 2a shows that such deprivation of oxygen also leads to a substantial decrease in total nucleotide content, chiefly because of a depletion of ATP, and results in a significant decrease in the ratio of ATP to ADP. Breakdown of ATP in our conditions for the incubation of the blastocysts can be expected, for enzymes able to dephosphorylate ATP are present in the rabbit endometrium as well as in blastocysts⁸. The apparent stability of ADP presumably results because ADP formed by the dephosphorylation of ATP may itself be used as an additional source of energy in anaerobic conditions.

Treatment of rabbits with antimetabolites such as 2-deoxyglucose, 6-mercaptopurine riboside, or 6-mercaptopurine, at certain strictly defined stages of early gestation, causes typical and histologically readily recognizable damage in the blastocysts⁷. In particular, maternally transmitted 2-deoxyglucose has been shown to act very rapidly but exclusively on the cells of the embryonic disk, leaving the much larger area of the trophoblast unscathed. In contrast to this, 6-mercaptopurine riboside and 6-mercaptopurine have a more generalized effect evident in all regions of the blastocysts.

With respect to the content of ATP and ADP in blastocysts, Table 2b shows that in response to 2-deoxyglucose, possibly because of the limited extent of its injuring effect, there was no distinct change in either total nucleotide content or the ratio of ATP to ADP. In blastocysts obtained from a rabbit treated with 6-mercaptopurine riboside there was a substantial reduction in the content of ATP, but not of ADP, resulting in a ratio of ATP to ADP of less than 1.0. In blastocysts collected from rabbits that had been given 6-mercaptopurine, short-term treatment (25 h) had no obvious effect, but the longer exposure (44 h) gave values for ATP and ADP which were low for the age of the embryos, presumably corresponding to the greater

Table 1 ATP and ADP in Rabbit Blastocysts recovered from Untreated Animals

	5 days		5 days + 9 h		Age of blastocysts (interval from time of mating) 6 days						6 days + 5 h		6 days + 9 h		6 days + 12 h	
	25	16	22	102	77	98	107	161	99	165	156	150	342	261	156	156
ATP	25	16	22	102	77	98	107	161	99	165	156	150	342	261	156	156
ADP	6	2	5	32	29	33	50	25	52	68	47	55	64	84	60	60
ATP + ADP	31	18	27	144	106	131	157	186	151	233	203	205	406	345	216	216
ATP/ADP	4.2	8.0	4.4	3.2	2.7	3.0	2.1	6.4	1.9	2.4	3.3	2.7	5.3	3.1	3.1	3.1

Results are expressed as pmol/blastocyst.

Table 2 ATP and ADP in Rabbit Blastocysts (pmol/embryo) after Treatment in Various Conditions*(a) in vitro*

	Control	Treated 60 min, 37° C	Control	Treated 120 min, 37° C
ATP	161	28	107	7
ADP	25	60	50	42
ATP + ADP	186	88	157	49
ATP/ADP	6.4	0.47	2.1	0.16

(b) in vivo

Maternal treatment Duration (h)	22	2-DG 24	24	6-MPR 42	25	6-MP 44
ATP	132	150	137	50	162	100
ADP	82	48	62	61	43	29
ATP + ADP	214	198	199	111	205	129
ATP/ADP	1.6	3.1	2.2	0.82	3.8	3.5

(a) Treatment in vitro, to examine the effect of hypoxia.

Blastocyst-bearing uterine horns dissected from two normal rabbits on day 6 of gestation were separated at the cervix; the blastocysts from one horn of each uterus were removed at once and frozen in solid CO₂ (control); the other horns were left unopened on saline-moistened filter paper in covered shallow Petri dishes, for 60 and 120 min, respectively, at 37°, and the blastocysts were processed at the end of incubation (treated).

(b) Treatment in vivo, after maternal administration of antimetabolites (2-DG, 2-deoxyglucose; 6-MPR, 6-mercaptopurine riboside; 6-MP, 6-mercaptopurine).

Pregnant rabbits were given single injections of 2-deoxyglucose (300 mg/kg) subcutaneously or intravenously; 6-mercaptopurine riboside (15 mg/kg) intravenously; 6-mercaptopurine (150 mg/kg) subcutaneously. The duration of treatment (hours elapsed from time of injection) is indicated in the table; the age of blastocysts at the termination of the experimental period was 6 days 6 h.

damage sustained by the blastocysts because of prolonged maternal treatment.

Our data indicate that, on purely methodological grounds, the luciferase assay of ATP and ADP is suitable for studies on early mammalian embryos; with minor modifications it could probably be scaled down to the level of individual rabbit blastocysts, or the much smaller blastocysts of other mammalian species. The ATP assay also gave satisfactory results with rabbit blastocysts that had been fixed in methanol. This would make it possible to combine chemical measurements with a histological examination of the embryos by the flat-mount procedure.

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Received July 21; revised September 1, 1970.

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Effects of Serotonin on Spontaneous Ovulation in Rats

THE hypothalamus is particularly rich in biogenic amines—serotonin, dopamine and norepinephrine—but their role in the reproductive processes is not well understood¹. Most of these amines are located in the nerve terminals many of which end in the region of the median eminence¹. In recent experiments infusion of dopamine into the third ventricle stimulated the release of luteinizing hormone (LH) whereas a similar infusion of serotonin decreased it². This has given rise to the speculation that dopamine may function as a transmitter for the release of luteinizing hormone releasing factor (LH-RF) while inhibitory influences may be mediated through serotonin. The latter possibility is supported by the fact that serotonin has inhibitory effects on ovulation induced by gonadotrophins in immature mice³ and rats⁴. We have now examined the effects of this amine on spontaneous ovulation in adult rats with a 4 day oestrous cycle.

Smears were taken daily from sexually mature rats of Alderley Park strain I, maintained in controlled conditions of light (from 0600 h to 2000 h) and temperature (22° C). Those with at least one 4 day oestrous cycle were included in the study. Serotonin (5-hydroxytryptamine creatinine sulphate) and related compounds (Sigma) or methysergide (Sandoz) were given in 0.5 ml. of saline. Rats were killed on the morning of expected oestrus and tubal ova per rat counted.

In replicate experiments, subcutaneous injection of serotonin (50 mg) at 1700 h on the day before pro-oestrus interfered with ovulation without affecting vaginal cornification (groups 2 and 2A). But the same treatment at 0930 h on the day of pro-oestrus—that is, before the critical period—was ineffective (group 3). When rats were pretreated with the serotonin antagonist, methysergide (25 mg), by intraperitoneal injection 0.5 h before the subcutaneous injection of serotonin on the day before pro-oestrus, there was no interference with ovulation (group 5). The antagonist alone in the absence of serotonin was inactive (group 6), as were 5-hydroxy-DL-tryptophan, a precursor of serotonin (group 7) and tryptophol, which is an intermediate metabolite of the same compound (group 8). These experiments demonstrate the specificity of serotonin and exclude the toxicity of the compound as a causative factor. There was no significant loss in body weight during the experimental period, although animals became sedated after the injection of serotonin. Smaller doses of serotonin (10 mg/kg, group 4) were inactive, probably because of the poor penetration of the amine across the blood brain barrier. Preliminary studies (unpublished) suggest that the inhibition of ovulation is associated with an increase in the hypothalamic concentration of serotonin, measured chemically. It is a matter of speculation whether or not exogenous serotonin inhibits ovulation by augmenting the effect of serotonergic fibres, which has been presumed to exercise restraint on the release of LH-RF² (and

Table 1 Effects of Serotonin Given Singly or in Combination with its Antagonist—Methysergide Hydrogen Maleate—on Ovulation in 4 Day Cyclic Rats

Group No. and treatment	Dose (mg/kg) and route	Day of cycle and time of injection	Rats ovulating	Ova per ovulating rat	Rats with cornified smears	Change in body weight (%)
			No. treated		No. treated	
1 Oestrous control	0	—	7/7	12.1 ± 0.5	7/7	+2.1
2 Serotonin	50, sc	Di-oestrus, 1700 h	0/4	0	4/4	-1.3
2A Serotonin	50, sc	Di-oestrus, 1700 h	3/7	1†	7/7	+0.1
3 Serotonin	50, sc	Pro-oestrus, 0930 h	3/4	10.3 ± 1.8	3/4	-1.7
4 Serotonin	10, sc	Di-oestrus, 1700 h	3/4	8.3 ± 1.7*	3/4	+1.3
5 Methysergide and serotonin	25, ip	Di-oestrus, 1630 h				
6 Methysergide	50, sc	Di-oestrus, 1700 h	4/4	12.0 ± 0.7	4/4	-3.8
7 5-Hydroxy-DL-tryptophan	25, ip	Di-oestrus, 1700 h	4/4	12.0 ± 0.7	4/4	-1.8
8 Tryptophol	50, sc	Di-oestrus, 1700 h	4/4	11.2 ± 0.7	4/4	0
	50, sc	Di-oestrus, 1700 h	3/4	11.7 ± 0.7	3/4	-2.4

Values are means ± s.e.

* $P < 0.05$ when compared with oestrous control.

† One egg without cumulus in each of three rats.

consequently of LH). It is not known whether the inhibitory effects on ovulation of oral contraceptives or antioestrogens⁵ are mediated by such a mechanism, although many of these agents are presumed to act at the hypothalamic level.

I thank Miss P. Maxwell for technical assistance.

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Control of Accept and Reject Reflexes in the Octopus

Food, such as a piece of fish, placed against the suckers of an octopus arm is usually transported to the mouth by a combination of arm and sucker movements, here termed the accept reflex. The opposite reflex, reject, involves passing food distally along the suckers to the arm tip and pushing it away¹. Rejection is less frequent in normal octopuses but can be enhanced by punishment for accepting objects placed against the suckers. This is the basis of tactile training experiments².

Amputated arms continue to make reflex responses to tactile stimulation^{1,3-5}. The accept reflex can almost always be elicited by placing small objects against the suckers but the reject reflex rarely occurs¹. Even so, it is assumed that both reflexes are organized by the arm nerve cord^{1,6}. In intact octopuses, two separate areas of the supraoesophageal lobes control arm movements (Fig. 1): the inferior frontal lobes organize feeding; the basal lobes, locomotion^{7,8}. The inferior frontal lobes may also control accept and reject reflexes^{6,8}. Animals with lesions in this region, however, can accept but apparently cannot reject^{8,9}. This contradiction may have arisen because information about rejection comes chiefly from training experiments, which test the ability to learn to reject an acceptable object. I have investigated the ability to

make the reject reflex by giving a noxious stimulus test to arms isolated from the central nervous system and to octopuses with lesions in the supraoesophageal lobes.

Procedures for selecting, keeping and operating on *Octopus vulgaris*, obtained from the Bay of Naples, are described elsewhere^{2,10}. Pieces of fresh, dead sardine, weighing 0.5 g, soaked in a 3% solution of quinine hydrochloride in distilled water were used as the noxious stimulus (NS). Identical pieces, untreated, were used as a control (S). A piece of fish was placed on the suckers midway along the arm and the response recorded as accept, reject, or refuse (that is, suckers would not hold the fish).

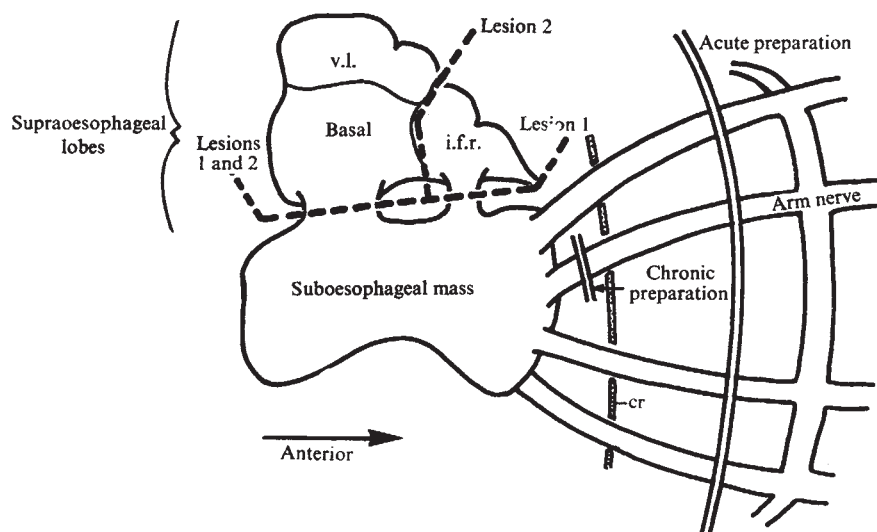
Arms were isolated from the central nervous system in two ways (Fig. 1), by amputation of the eight arms together from unanaesthetized octopuses (acute preparations) or by denervating a single arm under anaesthetic (chronic preparation)¹⁰. Each preparation received four tests in the order S, NS, NS, S. In acute preparations, S was accepted in sixteen tests out of eighteen, with no rejections. NS was accepted once, rejected ten times and refused eight times. In chronic preparations the reaction of the denervated arms to the NS test was a sharp withdrawal of the suckers, which refused to hold the fish. Nevertheless, in seven out of thirteen tests the arm bent at the level stimulated in a typical accept reflex. S was accepted on eleven tests, refused on three but never rejected. These tests indicate that both reflexes are organized in the arm nerve cord but suggest that reject is less easily elicited than accept.

To investigate central control of the reflexes, anaesthetized octopuses were blinded by section of the optic nerve, to facilitate tactile testing², and lesions were made in the supraoesophageal lobes. After 24 h recovery, they were given one test session a day for 4 days, with tests in the order NS, S, S, NS. Left and right arms were tested alternately and the side tested was changed each day. Because asymmetrical lesions produce asymmetrical behaviour¹, results from left and right arms were treated separately throughout. The extent of the lesions was determined post-mortem by reconstruction from serial sections.

In preliminary tests on animals with supraoesophageal lobes removed on one side of the brain only, the ipsilateral arms made abortive rejections: that is, the arm tested accepted but the sardine was rejected when it reached the mouth or touched the contralateral arms. The contralateral arms rejected typically when tested.

The importance of the inferior frontal system in the control of rejection was confirmed by comparing a group with all the supraoesophageal lobes removed (Fig. 1, lesion 1) with a group in which all the supraoesophageal lobes except the inferior frontal lobes were removed (Fig. 1, lesion 2). Animals with the inferior frontal lobes intact rejected the NS, while those without inferior frontal lobes usually accepted NS as well as S (Table 1). Although both accept and reject are

Fig. 1 Diagram of the central nervous system of *Octopus*. The level at which the arms were amputated (acute preparation) or denervated (chronic preparation) and the lesions in the supra-oesophageal lobes are shown. Lesion 1: all supra-oesophageal lobes removed; lesion 2: all supra-oesophageal lobes removed except the inferior frontal region (i.f.r.); cr, cranial cartilage; v.l.=vertical and associated lobes.



organized by the arm nerve cord, the inferior frontal lobe must be necessary for the performance of the reject reflex.

The inferior frontal region is a complex of five lobes, including the superior buccal lobe (Fig. 2). A second series of lesions was made to discover which of these control the reject reflex. It is impossible to remove discrete areas of the region without damaging other lobes or their tracts. Instead, varying amounts of inferior frontal tissue were removed from a series of animals and ability to reject was correlated with the sites of the lesions. Seven animals were given NS tests. A further eight, which were tested only with S, have been considered because they either rejected or made abortive rejections.

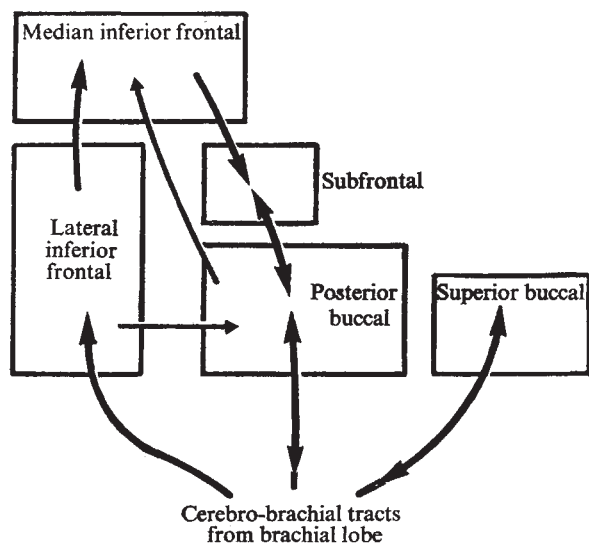


Fig. 2 Diagram of the lobes of the inferior frontal region exploded to show the main pathways associated with the arms. The lateral inferior frontal lobe normally flanks the posterior buccal and subfrontal lobes (based on Young¹¹).

Separate tracts connect the superior buccal, posterior buccal and lateral inferior frontal lobes to the brachial lobe in the suboesophageal mass (Fig. 2)¹¹. Three animals had large lesions (more than 50% of the lobe removed) in the superior buccal lobe and four had large lesions in the lateral inferior frontal lobe. All were able to reject. Conversely, eight out of nine animals with large lesions in the posterior buccal lobe failed to reject. This restricts the control of rejection to the

posterior buccal, subfrontal and median inferior frontal lobes, which have their connexions in the posterior buccal-brachial tract. The latter two lobes can also be eliminated. Twelve animals had large lesions in the median inferior frontal lobe although the pathways through the posterior buccal and lateral inferior frontal lobes were intact. Ten were able to reject, including six with the lobe completely absent. Similarly, all four animals with large lesions in the subfrontal lobe rejected correctly.

Table 1 Noxious Stimulus Experiment: Large Supraoesophageal Lesions

	Sardine (S)			Noxious stimulus (NS)		
	Accept	Reject	Refuse	Accept	Reject	Refuse
Lesion 1	32	0	0	23	1	8
Lesion 2	30	1	2	7	22	1

The difference in treatment of sardine and the noxious stimulus by the group with lesion 2 is highly significant ($\chi^2 = 30.44$, 2×2 contingency test).

This indicates that the posterior buccal lobe controls rejection. The results from two animals suggest that only a small part of the lobe is involved. These made abortive rejections with the right arms but rejected normally with the left. The lesions were restricted to the medial, posterior part of the posterior buccal lobe and the ventral subfrontal lobe on the right. In contrast, nine animals with lesions involving less than 25% of the dorsal or anterior parts of the posterior buccal lobe rejected correctly. The medial, posterior part of the posterior buccal lobe, however, is confluent with the ventral subfrontal lobe. No animal had one of these areas removed completely without damaging the other. This makes it impossible to determine whether the cells essential for rejection are in the posterior buccal or subfrontal.

This part of the posterior buccal and subfrontal lobes appears to function by controlling the bias towards the accept reflex, so that the reject reflex appears only in response to noxious stimulation. This fits with Young's hypothesis¹¹ that the tactile memory system, in which the subfrontal lobe is essential, evolved as an elaboration of the control of reflex arm movements by the posterior buccal lobe. It is not clear whether this control is achieved by exciting the reject reflex or by inhibiting the accept reflex so that the reject reflex can be made.

I thank Professor J. Z. Young and Dr M. J. Wells for helpful discussion and the director and staff of the Stazione Zoologica, Naples, for the use of facilities. The work was supported by

an SRC research studentship and the Oxford University Naples scholarship.

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Received June 17; revised September 9, 1970.

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Transduction Processes of Movement and Position Sensitive Cells in a Crustacean Limb Proprioceptor

DURING the past few years a great deal of work has been done on the physiology of crustacean limb proprioceptors. The study reported here involved ultrastructural differences between functionally distinct cells in the propodite-dactylopodite (PD) chordotonal organ of *Cancer pagurus*, and was based on serial transverse sections. Final details will be published elsewhere.

The PD organ monitors the relationship between the two most distal leg joints (dactylopodite and propodite)^{1,2}. It consists of numerous sensory cells with dendrites which are embedded in a strand of tissue containing collagen and supporting cells. Some sensory cells monitor position, others movement, and others are intermediate¹⁻³. The sensory cells are paired: each scolopidium contains a ciliary dendrite and a paraciliary dendrite^{4,5}, which are structurally different.

Interest has centred on the way in which some movement-sensitive cells respond to strand extension (elongation-sensitive cells or ESCs) while others respond to strand relaxation (relaxation-sensitive cells or RSCs). Previous theories were based on the idea that one dendrite in each scolopidium was an ESC and the other an RSC⁵, and usually suggested that bending of the distal region of the scolopidium had a differential effect on the two dendrites⁶⁻⁸. A study of the PD organ in *Cancer irroratus*³, however, indicated that both dendrites of any given scolopidium respond to the same direction of stimulation, and that the RSCs insert into the dorsal surface and the ESCs into the anterior surface of the strand. These movement-sensitive cells all tend to have large cell bodies (40–60 μ m) associated with the more proximal part of the strand, while the position-sensitive cells have smaller cell bodies (10–20 μ m) situated more distally^{2,3}.

In both movement and position scolopidia the terminal regions of both dendrites are surrounded by a scolopale cell which is surrounded by a pair of sheathing cells, one or both of which may be in continuity with the scolopale cell. The scolopale cell contains an electron-dense matrix which surrounds numerous longitudinally oriented microtubules. This is the scolopale. In certain places the matrix is juxtaposed to the inner wall of the scolopale cell and makes desmosome contacts (attachment plaques) with the dendrites in the region of their axial filaments (Fig. 1A). Distal to the scolopale the

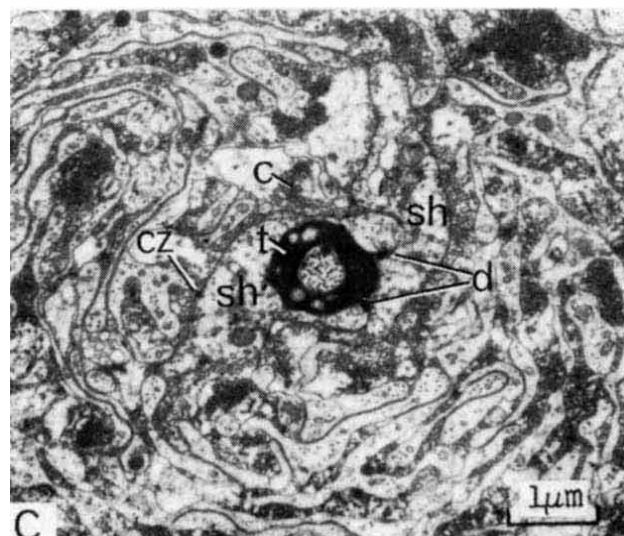
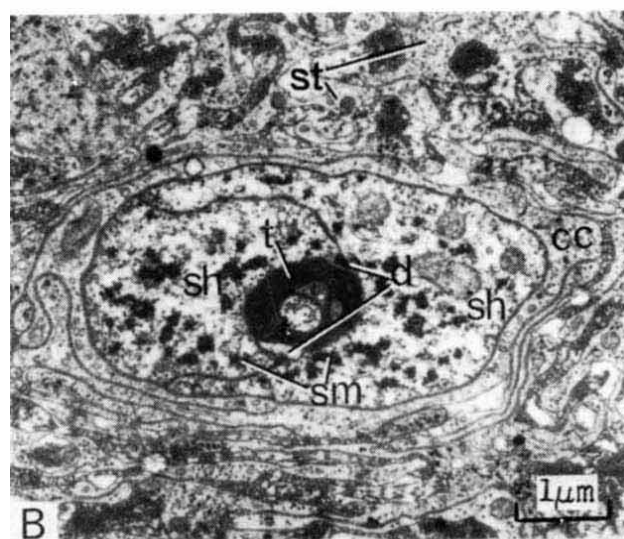
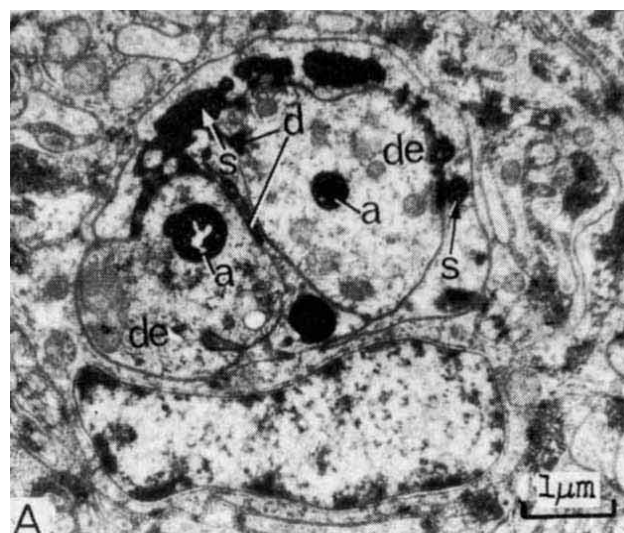


Fig. 1 Electromicrographs of transverse sections of the PD organ. A, The scolopale region of an ESC scolopidium to show the desmosome contacts (d) between the scolopale (s) and the dendrites (de) in the region of their axial filaments (a). B, The tube region of an ESC scolopidium to show the dendrites in their tube (t) surrounded by a pair of sheathing cells (sh) and a cap cell (cc). sm, Scolopale-like material; st, strand cell. C, The tube region of an RSC scolopidium to show the dendrites in their tube surrounded by the sheathing cells and the close proximity of the collagen (c). cz, Contact zone.

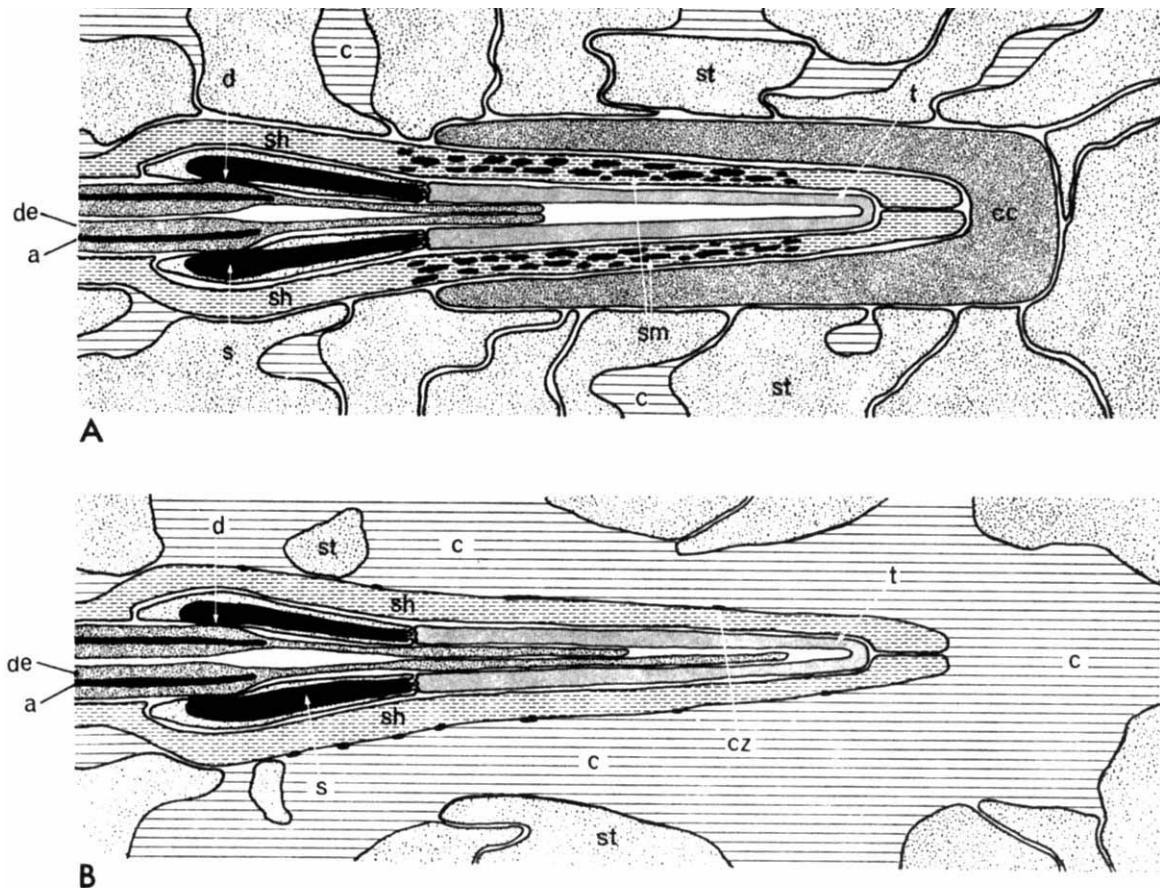


Fig. 2 Diagrammatic longitudinal sections through (A) ESC and (B) RSC scolopidia. Abbreviations are as in Fig. 1.

dendrites enter a long extracellular "tube" of electron-dense material, which is also surrounded by sheathing cells which are firmly attached to one another by desmosomes close to the tube which is thus held firmly in position (Fig. 1B and C).

If the stretch of the dendritic endings is the adequate stimulus⁶⁻⁸, the dendritic terminals must move relative to some fixed point further back along the dendrite. Such a fixed point is provided by the desmosome contacts between the dendrites and the scolopale. Distally the dendrites appear to fit the tube fairly closely, so that differences between cells sensitive to movement and position can be explained in terms of the potential friction between the dendrites and the tube walls. Movement of the tube away from the fixed point will stretch the dendrites. In position units the friction will be high and the dendrites will remain stretched; whereas in movement units the friction developed is less and they will slip back to their original position. For intermediate units an intermediate situation will prevail.

Apart from differences in dendritic structure there are two overriding differences between ESC and RSC scolopidia. In RSCs the sheathing cells are in direct contact with the collagen-containing matrix of the strand (Fig. 1B), whereas in ESCs there is a special "cap" cell in the tube region which surrounds the sheathing cells and is in contact over almost all of its surface with processes of the strand cells. The second difference is that in ESC scolopidia the sheathing cells in the region of the tube contain areas of electron-dense material resembling the scolopale material which surrounds longitudinally oriented microtubules.

We suggest that in ESC scolopidia the tube and the fixed point in the scolopale region move away from each other, thus stretching the dendritic terminations, because the scolopidium is attached to the cellular network of the strand and any

stretching of the strand is equally distributed among all cellular components (Fig. 2A).

The situation is rather more complex in the case of the RSC scolopidia. Here there is no contact of the tube sheathing cells with any cellular material to any noticeable extent. When the strand relaxes, however, the energy released by the relaxation of the collagen molecules may result in a rebound effect, forcing the fixed point in the scolopale region slightly away from the tube region. This is possible because the sheathing cells taper distally along the length of the tube and so present an angle to the longitudinally oriented collagen molecules (Fig. 2B). The collagen molecules can moreover be seen to make contact with the sheathing cells at various points (Fig. 1C). This effect must be small, which implies that the RSCs are more sensitive than the ESCs. The greater length of the dendritic terminations in the RSC scolopidia probably contributes to this sensitivity. We consider that the strengthening material in the sheathing cells of the ESC scolopidia helps to maintain a rather rigid system, so preventing lateral displacement which might stretch the dendrites. Because there is no direct contact with the cellular network of the strand, the strengthening material would not be required in the sheathing cells of the RSC scolopidia, and its absence may help to increase their sensitivity. Finally, the different structure of the two dendrites in each pair may be a reflexion of their differing sensitivities, as Hartman and Boettiger suggested³.

We thank Dr K. M. Rudall for useful discussion. This work was supported by a grant from the SRC to P. J. M.

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Received July 28, 1970.

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Sharp Increase in Free Circulating Oestrogens Immediately Before Parturition in Sheep

THE principal oestrogen secreted by the ovary of the non-pregnant ewe is 17β -oestradiol¹. After continuous infusion of ^3H - 17β -oestradiol into both pregnant and non-pregnant sheep, oestrone and 17α -oestradiol have been isolated from blood as the chief unconjugated radiometabolites^{2,3}. In pregnancy, oestrogens are excreted in urine as oestrone and 17α -oestradiol conjugates⁴, but calculation of blood steroid concentration from these data⁴ and from the metabolic clearance rate of 17β -oestradiol² suggested that the circulating concentration of 17β -oestradiol in the pregnant sheep would be extremely small (<20 pg/ml. of plasma). Measurements, therefore, of this steroid in circulating blood of the sheep have not been reported, and the role of oestrogens in late pregnancy and parturition has not been defined clearly. Because a decreasing progesterone block on the myometrial contractile response to oxytocin cannot always account for the onset of parturition⁵, it has become increasingly important to establish any significant changes in oestrogen biosynthesis in late pregnancy. I wish to report a rapid ten-fold increase in the maternal circulating oestrogen on the day before parturition in the sheep, which could provide a positive trigger for the onset of labour.

The method is based on the radioimmunoassay of Caldwell, Scaramuzzi, Tillson and Thorneycroft⁶, which uses an antiserum prepared against 17β -oestradiol, but which in our laboratory showed a cross reaction against oestrone (92%) and 17α -oestradiol (36%). The results reported here will be referred to as the values for total unconjugated oestrogens extracted from blood. Unconjugated steroid is generally thought to be the chief biologically active fraction within the total blood pool.

Fig. 1 shows plasma total oestrogens (pg/ml.) throughout seven pregnancies in five sheep; the day of parturition has been taken as day 0. The concentration of oestrogens was less than 5 pg/ml. until day -31, after which it increased slowly to 20-40 pg/ml. by day -5. In samples taken the day before parturition or on the day of lambing, a peak of free oestrogen concentration was found which varied between 75 pg/ml. and 411 pg/ml., the latter figure being the mean of six samples taken from one sheep between 0 and 35 h before birth. By 5 h after birth the concentration of oestrogen in one sheep had already decreased to 35 pg/ml. from 75 pg/ml. the previous day, and in all but one animal, oestrogens were not detectable by the first day after birth.

Although the actual period of gestation in this series varied between 138 and 148 days, in animals from which samples were taken at lambing there was a marked increase in maternal circulating oestrogens on that day or the preceding day. The concentration of progesterone in the blood is decreasing by this time⁷, and so such an alteration in steroid ratio may be involved in the stimulation of the release of oxytocin⁸, or in the preconditioning of the myometrium to its

effects, possibly by modifying the electrolyte balance⁹. It has been postulated that the increased activity of the sheep foetal adrenal gland, which begins 5 days pre-partum, may be involved in the initiation of parturition¹⁰. This gland may also be involved in the secretion of increased amounts of neutral steroid precursors for placental oestrogen¹¹ biosynthesis, using the placental aromatizing enzyme systems. The results reported here suggest that any hypothesis of a foetal-induced mechanism of parturition in the sheep must take into account the very rapid increase in circulating maternal oestrogens that occurs within 2 days of lambing.

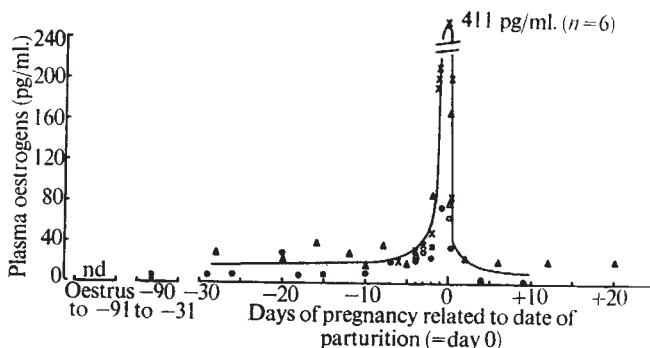


Fig. 1 Oestrogens in sheep peripheral plasma during pregnancy. nd, Not detected $n=12$. ●, Sheep Jane, lambing 1970, gestation 144 days; ○, Jane, 1969, 143; ▲, Di, 1970, 145; △, Di, 1969, 138; ×, Millicent, 1970, 145; ■, Isabella, 1970, 148. The peak of 411 pg is the mean of six samples taken between -35 and +1 h in sheep Millicent.

I thank Dr R. B. Heap and Mr F. A. Harrison for advice and interest, and Mr A. Henville for technical assistance. The antiserum to 17β -oestradiol was given by Dr B. V. Caldwell, Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts. This work was supported by a grant from the Science Research Council.

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Received August 3; revised October 13, 1970.

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BOOK REVIEWS

Informed Sources

The Growth of Parliamentary Scrutiny by Committee. Edited by Alfred Morris. With essays by seven other MPs of the 1966–70 Parliament. (The Commonwealth and International Library of Science, Technology, Engineering and Liberal Studies.) Pp. xi + 141. (Pergamon: Oxford and New York, November 1970.) 50s, \$8 boards; 35s, \$5.50 paper.

THE Chamber of the House of Commons is, to some, a focal point for political debate—the place where informed politicians engage in the cut and thrust of argument about the vital issues of the day. But to those of a less romantic disposition, it is a centre of bickering and mutual backbiting by Members of Parliament frequently ignorant of the full information behind the decisions they take. This picture usually goes hand-in-hand with the idea that Parliament is no longer the centre of power in Britain because the important issues are decided in the Cabinet office or even behind the locked doors of Whitehall committee rooms.

That is what the book is all about. It is a collection of essays by members of the previous Parliament on the merits and pitfalls in the expansion of the select committee system during the past five years. It is, in effect, a symposium on the power of the legislature to check the actions and policies of the executive. But it is rather a one-sided publication—six of the seven contributors have been members or even chairmen of select committees, and only John Mendelson is there on the side of the romantics to put the viewpoint that the select committees may undermine the power of the legislature to take important decisions.

The burden of Mr Mendelson's eloquent argument is that an extension of the select committee system will be a step on the road to consensus politics. He deplores the idea that some issues can be taken "out of politics" and decided in the more congenial atmosphere of committee rooms. He argues that a select committee on, for example, defence matters would inevitably lead to first and second class MPs in defence debates and that this situation would make something of a farce of parliamentary procedure. Like many of his friends, Mr Mendelson rightly views with some alarm any drift in Britain towards a system of government by committee, and he uses the example of the United States to point out the pitfalls in such a development.

But this argument to some extent begs the question of how Members of Parlia-

ment can avail themselves of the information necessary to make political decisions. Mr Mendelson's suggestion that every MP should have a research officer, for example, really does not go far enough—there would still be a need for the sort of deep probings that only a formal committee of the House of Commons is capable of undertaking. It is, in fact, a severe indictment of the British Parliamentary system that members are still labouring under the sort of difficulties which were arising at the end of the last century—a research officer and a personal office are the least that could be done to ensure that members of Parliament can carry out their Parliamentary duties efficiently.

The difficulties which Members of Parliament may find in appreciating the full consequences of decisions taken in the field of science and technology epitomize the nineteenth century atmosphere which still exists in Westminster, and the essay by Mr Arthur Palmer, the capable and respected chairman of the Select Committee on Science and Technology in the previous Parliament, hammers this point home. This particular select committee has already done much to make members of Parliament and the general public aware of some of the consequences of government policies on science and technology; the intention outlined in the recent Green Paper on Select Committees to retain the Select Committee on Science and Technology is therefore to be applauded.

Sceptics of the select committee system often point out that the demands made on members' time cannot support an expansion of the system without detracting from the work of the standing committees of the House of Commons, but Mr Palmer has an answer. He suggests that many of the non-controversial bills relating to science and technology could be referred to the Select Committee instead of to standing committees. This is an attractive proposition in many ways, but it is unlikely to appeal to the sceptics who would argue that there are few parliamentary issues that are entirely noncontroversial; to refer bills to select committees would be giving way to consensus politics.

Whatever the outcome of the debate about the extension of the select committee system initiated in 1966 by Mr Crossman and Mr Peart, it seems likely that several select committees are here to stay. Until the romantics can provide strong evidence to refute the suggestion that the Chamber of the House of Commons is nothing more than the stage for debates the outcome of which can be

predicted well in advance, this situation is desirable.

COLIN NORMAN

Ethnic Diversity

Problems in Human Biology: A Study of Brazilian Populations. By F. M. Salzano and N. Freire-Maia. Pp. 200. (Wayne State University: Detroit, March 1970.) \$8.95.

FOR the first half of this century human genetics was a rather restricted discipline; in the second half it is rapidly assuming the central position in the spectrum of studies which comprise "human biology". Not only is its subject matter of central interest in the wider discipline, but many of the statistical techniques which are now rejuvenating human biology have their origin in human genetics.

Drawing extensively from demography, anthropology and history, as well as from their own subject, two Brazilian geneticists present in this book a survey of the Brazilian population. It is a model exposition, readable, concise and up-to-date. Those contemplating similar studies on other populations would do well to use this book as a guide.

The inhabitants of Brazil currently constitute perhaps the most interesting of all human populations by virtue of their numbers, their rapid rate of growth, the great ethnic diversity of their ancestors coupled with the degree of interracial crossing, and the continued presence of primitive Indian groups. In the compass of two hundred pages the authors examine this heterogeneous population from many points of view, exposing not only the facts of migration and marriage, fertility and gene frequency, but also their devotion to the people they are studying. It is a warm and sympathetic book of interest to far more than Latin-American specialists. The authors' attitude to racial intolerance is an object lesson to those students of human society who would have us believe that moral equality is based upon biological similarity, for Dr Salzano's and Dr Freire-Maia's book is essentially concerned with biological heterogeneity, and until we learn to understand and respect each other's differences as well as each other's similarities, prejudice will not be stilled.

The present edition is a good translation from the Portuguese; the only word which I found mysterious was *epopee*, which the authors use for the great Portuguese maritime expansion, but which, according to the Shorter Oxford English Dictionary, is an epic poem.

A. W. F. EDWARDS

Marx on Hegel

Critique of Hegel's "Philosophy of Right". By Karl Marx. Edited by Joseph O'Malley with an introduction and notes. Translated from the German by Annette Jolin and Joseph O'Malley. Pp. lxxvii+151. (Cambridge University: London, December 1970.) 55s; \$9.50.

THOSE interested in the philosophical basis of Marx's political and social writings will find this work of value. It is a translation of Marx's critical commentary on paragraphs 261-313 of Hegel's *Philosophy of Right*, and is popularly referred to as Marx's *Critique*. It was probably written in 1843, when Marx was 25. Although extracts of this work have previously been translated into English, Joseph O'Malley and Annette Jolin are the first to have attempted a complete translation. O'Malley has added an excellent introduction with many useful bibliographical references.

In the *Critique*, Marx brilliantly criticizes Hegel's attempt in the *Philosophy of Right* to justify the Prussian State in terms of his "Philosophy of the Absolute". Marx effectively exposes what he calls the pantheistic mystification of Hegel's method. His critical technique is based on Ludwig Feuerbach's insight that speculative philosophy, and in particular Hegelian philosophy, transposes subject and predicate so reducing man to a mere mode or predicate of the Absolute Idea, whereas he is, and ought to be, the subject. Hegel, Marx holds, uses political actuality as a mere illustration for his logic, and therefore misses its significance and leaves its contradictions unreconciled. But the task of philosophy, according to Marx, is to clarify such contradictions; and this is where his historico-genetic method comes in, for in tracing the historical development of political and social institutions their meaning becomes clear. In the *Critique* Marx therefore gives more than a critical analysis of Hegel's method. As the work progresses, more and more space is given to historical data and to expositions of his doctrinal attitudes, for example, on private property.

Marx accepts as true, however, the contradictions which feature in Hegel's analysis between the private, or civil, and the universal, or political, spheres. As O'Malley points out in his introduction, both Marx and Hegel are inheritors of Rousseau's problem: how is private interest to be reconciled with the general, or *l'homme* with *le citoyen*. Furthermore, Marx accepts Hegel's basic doctrine of the state as the embodiment of rational freedom. In other words, for both there is an ideal dimension to man, that of freedom, morality, social life; in short, the state. For Marx, this sets the standard by which to judge social and political institutions. The portmanteau-term that Marx uses in this connexion is

one originally put forward by Feuerbach, that of the "species-being" (*Gattungswesen*), which Marx uses in the sense, roughly, of one who is aware of himself as a member of a species, and thus has an idea of what it means to be a human being. He is thus able to maintain that there is an implicit rational and ethical content in social and political life, so that philosophy in its proper role of *praxis* is able to find the criterion by which to judge institutions, within empirical reality.

The *Critique* is salutary reading for anyone who may be inclined to forget just how firmly Marx's doctrine is set within the same tradition as Hegel's.

WOLFE MAYES

Scales in Sea

Sounds of Western North Atlantic Fishes: a Reference File of Biological Underwater Sounds. By Marie Poland Fish and William H. Mowbray. Pp. xx+207. (Johns Hopkins: Baltimore, Maryland and London, December 1970.) 119s.

SINCE at least the days of Aristotle, men have known that some fish are capable of making a noise audible in the air. In the *Historia Animalium* book 4, 9, Aristotle cited a number of Greek fishes which made piping sounds when captured. One described as a "sciaena", possibly the meagre *Argyrosomus regius*, grunted, while another, identified as the cuckoo gurnard (*Aspitrigla cuculus*), by D'Arcy Thompson in his translation of Aristotle, was said to make a noise like the cuckoo. Knowledge of fish noises advanced slowly, but in the nineteenth century a number of studies, notably those by Sorensen in 1895, and Dufossé in 1874, demonstrated the significance of sound production underwater and explored the anatomy of some of the better known sonic fishes. Until the beginning of the second world war most of the literature on the subject dealt with the more notable sound producers, such as the American Atlantic coast oyster toadfish (*Opsanus tau*), and the common failure to appreciate the level of noise in the sea gave rise to popular phrases like "the silent sea" well into the 1950s.

It was the second world war with the increasing sensitivity of underwater listening devices that focused attention on the variety of sounds underwater and the potential of several phyla of marine animals to produce noise. The majority of marine soundmakers that have been identified are fishes, and *Sounds of Western North Atlantic Fishes* is a collected album of fish noises. The basic research has been conducted under a contract from the US Navy, which clearly has a particular interest in the identification and physical description of underwater noises.

In this work Marie Poland Fish and William H. Mowbray present a report on

the sound-making capabilities of 220 species, from 59 families of fish found on the Atlantic and Caribbean coasts of the United States. The catalogue is arranged in systematic order, under familial and scientific names. Notes on the distribution, size and biology of each species are given, together with a verbal description of the noises produced in test tanks, and occasionally, where possible, in the wild. Notes on the sonic mechanisms involved have been included. Where this atlas differs from previous work is that in addition to describing the clicks, bumps, purrs, and thumps which these fish produce, these data are reproduced in spectrogram and oscillogram form for every species described. In this way, the description of fish sounds in the area has been placed on a firm physical basis and the way is clear for comparative studies of other species, and in other oceans.

As a work of reference it is invaluable. It is not without some frivolous interest, for, as the authors point out, fish use noises for much the same reasons as land-living vertebrates. Increased loquacity in the breeding season, sounds for offence, intimidation, and warning, are observable in their vocabularies, and it can be no surprise that the authors report that an enormous jewfish (*Epinephelus itajara*), more than 1.8 metres in length, when prodded in its pen emitted a "tremendous boom, sometimes with two smaller grunts following". ALWYNE WHEELER

Immune Responses

Cellular Immunology. Books One and Two. By Sir Macfarlane Burnet. Pp. ix+726. (Melbourne University: Carlton, Victoria; Cambridge University: London, 1969.) 110s.

Immunological Surveillance. By Sir Macfarlane Burnet. Pp. 280. (Pergamon: Oxford, London and New York, November 1970.) 60s.

SINCE his "retirement" Sir Macfarlane Burnet has been, if anything, more productive than in the later years of his administrative responsibility. He has on his own admission attempted to sit back and review the work of others, though largely against the background of the various theories he has propounded. The results are presented as a massive compendium on cellular immunology together with a briefer exposé of the possible role of immunological surveillance mechanisms active against malignant cell populations. Burnet's views are always presented in an intensely personal manner. His confidence is sometimes infective, on other occasions exasperating—rarely is the reader left unmoved.

Cellular Immunology comprises two volumes, one of which has been issued separately as *Self and Non-Self*. The same material is looked at first in a semi-

popular style with relatively little attempt to argue and document, and second, in a more discursive manner. This format makes it possible to refer back and forth to the two levels of understanding—often a profitable exercise. The development of cellular immunology is accurately traced but a clear statement of the present position is often lacking. For this latter deficiency Burnet cannot be held wholly to blame; he is clearly an avid reader of the literature and in touch with many unpublished new experiments (particularly Australian) in a rapidly moving field; his doctrinaire approach, however, seems to have tempted him to ignore almost completely the phenomenon of cellular cooperation in the production of antibody which is presently so exciting for immunologists. The sort of experiments in which cooperation occurs (particularly between thymus and bone marrow-derived cells) are dismissed somewhat curtly as laboratory exercises, less likely to give significant results than the “experiments of nature” which are presented by the various congenital deficiencies of the immune system in man.

The material in *Immunological Surveillance* in some ways duplicates what is said in the other book. If anything, it is presented from a more emphatic viewpoint. Burnet seems to be trying to restrain his self-confessed and long-rooted capacity for making generalizations but without much success. We are told in the same paragraph (p. 6) that it is axiomatic (which the Oxford English Dictionary defines as “a self-evident truth”) that “transplantation of a spontaneous primary tumour to another host follows the same rules as transplantation of normal skin”. Two lines later we find “No biological statement can ever be made in absolutes”. Perhaps this is a simple linguistic problem, but Burnet makes much use of the word axiomatic and it is difficult to credit that he always means “it is assumed that”.

With this said it must be pointed out that both books abound in brilliant new ideas. Any research immunologist looking for a problem might well browse here, but let him beware of the premises on which Burnet bases his arguments; it is not easy to disentangle fact from the products of Burnet's fertile imagination. There are many instances of Burnet's laconic humour and increasing evidence that he is to be thought of as a humanist first and scientist second (for example, p. 120, *Immunological Surveillance*).

As biology becomes more diversified and its devotees more bewildered at the range of facts that they are expected to encompass, the numbers of great all-rounders like Burnet must steadily dwindle. Although he says that he has avoided the great conundrums of biology—the mechanisms of evolution, the relation between brain and mind and so

on—he is avowedly concerned with “immunity, growth, ageing, cancer and autoimmunity” (p. 50, *Immunological Surveillance*); far more than enough for most men and, in time, too much for any single mind. Burnet's books should be read with awe at their scholarship but not with unthinking belief as *ex cathedra* utterances, for herein lies both their great strength and their weakness.

A. J. S. DAVIES

Insect Gametogenesis

L'Influence des Stimuli Externes sur la Gamétogenèse des Insectes. (Colloques Internationaux du Centre National de la Recherche Scientifique, Tours, 9–13 Septembre 1969.) Pp. 422. (Editions du Centre National de la Recherche Scientifique, 1970.) 64.50 francs.

It has long been realized that the reproductive activities of insects are not only regulated to accord with the seasons but also limited by nutrition. Only in comparatively recent years has it become understood that reproduction may be controlled by the environment so that the rate of increase in a population is limited to a level that the environment can sustain.

Many examples of the adaptive control of reproduction are brought out in this symposium volume. Many parasitic insects retain and even resorb their eggs if there is a deficiency of hosts (Labeyrie, Onillon). Overcrowding among locusts leads to a change of “phase”; the gregarious migratory phase that results has a lowered reproductive rate (Papillon, Cassier). In ant societies the queen exerts a “psychosomatic” influence on the reproductive activity of the workers: their reproduction is either totally suppressed, or they produce small eggs incapable of development which are used as food for the larvae. In the absence of the queen, normal eggs are laid and, as they are unfertilized, give rise to males (Brian, Passera). The beet moth *Scrobipalpa* commonly reabsorbs the eggs in the absence of sugar beet; in the presence of the host plant, copulation and ovogenesis are stimulated and this leads to a rapid infestation of the crop (Robert). Effects of this kind are very frequent though not universal among Lepidoptera (Deseö). The various stimuli may promote copulation; the spermatozoa, acting through the sensory nervous system, can then activate the corpora allata. On the other hand, it may be that olfactory stimuli have the same effect (Benz).

Other contributions record the many ways in which reproduction can be influenced by external stimuli. In those Hemiptera, such as the bed bug, which practise “traumatic insemination”, it is the arrival of the spermatozoa in the ovary which evokes the gonadotropic secretion of the corpus allatum (Car-

yon). Copulation (Davey) or the presence of an introduced spermatophore (Engelmann) commonly stimulates oogenesis; in cockroaches the presence of a ripening egg capsule in the brood chamber inhibits the ripening of more eggs (Roth). These and other effects, such as the loss of sexual receptivity by the female *Drosophila* after mating, are generally exercised by way of the endocrine system, and usually via the corpus allatum or the neurosecretory cells in the brain (Merle, Joly). Finally, the deliberate pollution of the environment with “chemosterilants” by human agency can throw the ovary itself into disarray (Landa).

V. B. WIGGLESWORTH

Fungal Biology

Introduction to Fungi. By John Webster. Pp. 424. (Cambridge University: London, November 1970.) 60s; \$10.50.

In reviewing and warmly recommending Alexopoulos's *Introductory Mycology*, Dr Ainsworth¹ wrote “If de Bary's *Morphology and Biology of the Fungi*, 1887, is taken as a standard, a satisfactory modern textbook of mycology has yet to be written, . . .”. That book has now been written. Professor J. Webster wrote his book with two aims in mind. First, to write an introduction to those fungi which are easily available in the living state and to give some indication of where they can be obtained. Second, to produce illustrations of the kind that a student could make for himself from simple preparations of living material, and to illustrate things which he can verify for himself. Nobody can argue that he has not been eminently successful in achieving these aims. Webster is a rare artist among mycologists and most of the many illustrations in the text are his own, an almost unique feature in modern biological texts. Few students will ever match his excellent line illustrations. It is difficult to single out any for praise, but to suggest that many bear comparison with those in Engler and Prantl's *Die Natürlichen Pflanzenfamilien* is enough.

The text follows the general purpose scheme of classification proposed by Ainsworth in 1966 and consists of a short chapter on the Myxomycota followed by four chapters on the Eumycota, one on each of the four sub-divisions Mastigomycotina, Zygomycotina, Ascomycotina and Basidiomycotina. Selected common genera from the various orders or families within each sub-division are considered and accounts given of their methods of development, reproduction and dispersal, physiology, nutrition, mating type behaviour and a wealth of other very up to date information such as control methods, if pathogens, fine structure and economic uses.

In a textbook of some 400 pages,

Webster has obviously had to be selective as to what fungi he included. In the preface he states that he is prepared to accept a criticism that no attempt has been made to deal with the Fungi Imperfecti as a group. Nobody should dare criticize him on that score. It is time that we all dealt with them, as he has attempted to do with some conidial states of the Ascomycotina. It is here that I would have welcomed a more personal authoritative touch with some further illustrations of the variety of conidial states possessed by such genera as *Leptosphaeria* and *Pleospora*, and even the briefest mention of the aquatic Hyphomycetes perhaps tenuously linked to his account of *Nectria*.

I would similarly have welcomed a lengthy introductory chapter covering more general aspects of comparative fungal biology for the benefit of the first year student and perhaps a fuller treatment of other groups such as the Blastocladales and Monoblepharidales. In the former, for example, only *Allomyces* and *Blastocladiella* are considered. One must admit that these two genera are what Professor Ralph Emerson would describe as ideal "performing fungi" for classwork but few of us have ever isolated "wild" *Allomyces* or *Blastocladiella* whereas representatives of the type genus *Blastocladiella* are as easy to obtain as *Saprolegnia*, if ponds or streams are "baited" with fruit.

The text is lucid and concise. The only point which the student might find confusing is the author's treatment of variety, *forma specialis* and physiological race in the Erysiphales and Uredinales. In *Erysiphe graminis* (p. 187) he equates physiological races with *formae speciales* and in *Puccinia graminis* (p. 373) uses the category of variety for its six pathogenic entities and physiological races for the various strains within each. At this level it would be preferable to consider the pathogenic entities on particular hosts as *formae speciales* (for example, *E. graminis* f. sp. *tritici* and *P. graminis* f. sp. *tritici*, and so on), each of which is divisible into a number of physiological races. The student may also be taken aback after reading that *Penicillium cyclopium* is "one of the Fungi Imperfecti not an Ascomycete" (p. 157) to find that the genus *Penicillium* is later (p. 205) considered in the Plectomycetes. It is a great pity that so many minor errors escaped detection in the final preparatory stages. The majority of these are misspellings and, in the main, these are associated with the figures. I suspect that the method of offset printing used has not always done justice, in terms of definition, to some of Webster's photographs.

In addition to being the most valuable introduction to the fungi, the text is also a reference work, as the bibliography of almost 1,000 references would suggest. It will undoubtedly replace the standard

degree level textbooks such as Alexopoulos's *Introductory Mycology* and, in detailing the amazing diversity of fungi, it will in many ways complement the more general approach adopted by Professor Burnett in his *Fundamentals of Mycology*. To have two textbooks of such quality as these within two years is an immense boost to British mycology.

H. J. HUDSON

¹ Ainsworth, G. C., *Trans. Br. mycol. Soc.*, 36, 270 (1953).

Rigor and Flexibility

Matter and Motion. By N. Feather. Pp. 195. (Penguin: Harmondsworth, Middlesex, 1970.) 15s.

Free-Electron Physics. By P. S. Farago. Pp. 269. (Penguin: Harmondsworth, Middlesex, 1970.) 30s.

THESE are two titles from a projected series of over fifty volumes written especially for undergraduate courses in physical sciences: about half of these books will be designed to provide a course of increasing flexibility in successive years.

Professor Feather's book is among those offered for first year use. Few would argue that this year is not, in many ways, the most important for degree courses in physical sciences, but unless the foundation is sound the superstructure may become insecure and distorted. Some readers will certainly regard *Matter and Motion* as more suitable for the science historian than for the practical scientist, for almost the whole of it is long established, and the text could have been reduced to a fraction of what there is by avoiding difficulties resolved for centuries, and the logic of their resolution.

Here my sympathies lie, without qualification, with Professor Feather. It is well known that physical science has, in recent years, lost some of its compelling interest for the young student, and it is not difficult to believe that an important factor in this disillusionment has been the unqualified and uncritical certainty which has marked much of what is to be mastered in the early years. By playing down what the valuable text by Cox fifty years ago described as the "Winning of the Principles", this approach has devalued its subject. Professor Feather's book not only provides a more wholesome approach but, given that his readers have not lost the art of following continuous prose, should lead both to a clearer understanding and to the pleasure of well developed argument. Many of the difficulties that students of physics encounter during a university course arise from failures clearly to understand the bases of the subject; there is no short cut to this level of understanding.

In Professor Farago's book we have clearly moved forward to the third year. *Free-Electron Physics* is very much a

specialized option. In scope and treatment the book is eminently suitable for use in a final year Honours stream today. Indeed, it is a subject where rigour at a suitable level is fairly close to the practical areas within which the topic is important.

A final point is raised, in particular by *Matter and Motion*. As a text for the determined and literate student, enough has already been written. But what of his teacher? No problem arises when teaching is mainly tutorial, where the students' reading forms the matter for discussion, but the book raises much more difficult questions if the traditional lecture is an important feature of teaching. Professor Feather can hardly be better in paraphrase, and one must doubt the value of running a second treatment, probably different in spirit and timing, in parallel with the systematic mastery of his book.

J. G. WILSON

Space Rocketry

Nuclear Engineering for Satellites and Rockets. By Horst Löb. (Thiemig-Taschenbücher, Band 36.) Pp. xvi+399. (Verlag Karl Thiemig KG: München, 1970.) 24.80 DM.

It is difficult to know just what market this book is intended for. Because of the side by side presentation in German and English, the customer is effectively getting a mere 200 page pocket book (7 inches × 4.5 inches) at a very high price. Technically, the volume is excellently produced, and it contains many high quality illustrations. But having gone so far, the overall quality is sadly reduced by the poor standard of much of the English, which in places reads so clearly as a literal word for word translation of the German that the effect is one of caricature—"Thin-film-cells of galliumarsenide and cadmiumsulphide are under development, with which areas up to some 1,000 m² could be covered after projects of Boeing" is a fairly typical example, and there are others which it would be kindest to ignore here.

Having deciphered the cryptic English (or in places resorted to my own translation of the original German) I have found a comprehensive survey of the field and its future possibilities. West Germany lies second only to the US in developing "unconventional" propulsion systems for spaceflight, so that the high quality of the original work described here is understandable. Still, engineers working on nuclear and electrical propulsion systems for rockets will already be acquainted with this work, while any layman able to overcome the linguistic barrier will almost certainly be out of his depth technically.

But science journalists may find this book of value, and so indirectly this work may benefit the general state of public knowledge on advanced space transportation systems.

JOHN GRIBBIN

CORRESPONDENCE

Medvedev's Complaint

SIR,—In his comments on the excerpt from Medvedev's book J. J. Bickerman evades mentioning the salient difference between Medvedev's case and his own (*Nature*, 228, 297; 1970). Whereas Bickerman's request was for funds (which seem to be scarce in all countries) Medvedev not only had to apply for permission to leave his country for a few days but had to do so in vain.

It is tempting to ask which of the two accounts deserves being classified as "subtle communist propaganda". However, such demagoguery against another political ideology should, in my opinion, not appear in a scientific journal like *Nature*.

On the other hand, I think that bureaucracy in *absurdum* should be attacked in all countries. Therefore I cannot agree with Bickerman's recommendation of acquiescence in all official decisions which are not in conflict with "the existing law". Stupidity is no crime, but that does not mean that stupid decisions are sacrosanct. Nor stupid comments.

Yours faithfully,

LARS E. FRANK

Rösvägen 15,
S-163 59 Spanga, Sweden

LSD and Learning

SIR,—I find it puzzling that R. and E. Miller could draw the conclusion that "there is no evidence of significant long-term impairment of learning attributable to LSD" (*Nature*, 228, 1107; 1970). Their own data show that 5 weeks after discontinuing LSD injections the controls, with 2.2 mean errors, did almost twice as well as the LSD treated mice which had 4.0 mean errors.

Seventeen weeks earlier both groups of mice had 4.3 mean errors, which means to me that the untreated mice, when finally tested did 98% better, while the LSD mice had learned almost nothing.

I find it especially puzzling that the authors, as indicated by their address, are apparently members of a department of mathematics.

Yours faithfully,

R. T. BARRETT

Flat 2,
Old Fore Street,
Sidmouth,
Devon

The Biologist's Dilemma

SIR,—In the report (*Nature*, 228, 900; 1970) on a recent meeting of the British Society for Social Responsibility in Science, Dr R. G. Edwards, discussing the circumstances justifying abortion, is quoted as arguing that "there is no clash between scientific and medical ethics if the rights of the patient and the foetus are safeguarded at all times" and further that "it should be up to the patient to decide whether or not the pregnancy should be terminated".

Perhaps it is arguable that the rights of a grossly defective foetus (though scarcely where there is no more than a statistical chance of abnormality) are best safeguarded by its destruction. But in all other cases the decision to abort requires a judgment of the rights of the foetus to its life against the rights of the mother to be rid of it. Granted that when there is a risk of serious harm to the mother her interests should be given precedence over those of the child, if the decision is to be left to the mother alone she will have to act as judge in her own cause against the interests of the child. That must surely be unacceptable, unless the child is to be allowed no rights to its life at all.

Furthermore, where the question of foetal abnormality arises, quite apart from her own emotional involvement, only very rarely will a mother have the expert knowledge needed for a proper assessment of the risks, or indeed to understand any medical or genetical advice that may be proffered. Whether or not to terminate in such cases is often a difficult medical decision, and it is not one which doctors should seek to evade by placing the responsibility on to the mother. She cannot be compelled against her will to submit to abortion, of course; but if she does ask for it, that is only one of several factors needing to be taken into consideration. After all, it is by no means unheard of for a woman in the sometimes psychologically difficult early months of pregnancy to become convinced, without any rational justification, that there will be something wrong with her baby. Is the decision then still "up to the mother", with no responsibility devolving upon the doctor asked to destroy the child?

Yours faithfully,

C. B. GOODHART

Gonville and Caius College,
Cambridge

Partial Hepatectomy

SIR,—A. Sakai performs a partial hepatectomy on one of a pair of rats connected by cross-circulation catheters, and observes an increased uptake of tritiated thymidine in the nuclei of liver cells from the second rat¹.

This result is explained most simply as a result of growth of the liver of the second rat, stimulated by the increased metabolic load presented to it after partial hepatectomy is performed on the partner. There is no need to postulate specific humoral factors.

Yours faithfully,

A. J. KNELL

King's College Hospital Medical School,
Denmark Hill,
London SE5

¹ Sakai, A., *Nature*, 228, 1186 (1970).

Reprint Communication

SIR,—Whilst fully agreeing with the suggestions on reprint distribution made recently by Kruskal and Savage¹ may I simply add that such a scheme will be of especial benefit when an author makes it a point to send reprints of his paper, particularly to those workers (cited in the bibliography) who reside in foreign and non-English speaking countries. Apart from the courtesy involved, this will be of immense benefit in terms of increasing prompt scientific awareness, especially in view of (a) the normal postal transit and hence delay in the journals arriving in foreign countries, (b) the apparent lack of ready and easy availability or accessibility of foreign periodicals in several of the non-centralized libraries, and (c) the perhaps natural inertia in reading through a foreign periodical due to the language problem. All these problems may be overcome when the reprint arrives by post directly at the desk of an interested, though pleasantly surprised scientist.

Yours faithfully,

CUPPAM DASARATHY

Research Center,
British Steel Corporation,
Port Talbot,
Glamorgan

¹ Kruskal, W., and Savage, I. R., *Nature*, 228, 888 (1970).

Obituary

M. G. J. Minnaert

PROFESSOR M. G. J. MINNAERT, director of the observatory at Sonnenborgh, Utrecht, from 1937 to 1963, died on October 26, 1970, at the age of seventy-seven.

His career as a solar physicist, the activity for which he is best known to astronomers, did not begin until he was over thirty. He started, in fact, as a botanist, graduating at the University of Ghent, but his wish to understand better the effects of light on plants led him to Leiden before the 1914-18 war to study physics; it was his support for the Flemish movement, especially during the war, that led to his exile in Holland and to his post at the Physics Institute in Utrecht as a solar physicist. Here he worked for some years under Julius, from whom, according to his own testimony, he learnt much in optics and practical physics. Inspired by the techniques of photographic spectrophotometry, which were at that time being developed in Utrecht by Ornstein, Moll and van Cittert, he was one of the first to measure intensity profiles of the Fraunhofer lines in the solar spectrum and to attempt to explain these by theoretical models. In the 1930s, he and his pupils achieved a steady improvement in the methods of photographic spectrophotometry and in our knowledge of Fraunhofer lines and how they are formed. Among many others things, they superseded Rowland's empirical estimates by objective measurements of total absorption; they clarified the role of Doppler effect and damping in Fraunhofer line formation; and they introduced astronomers to the "curve of growth", the curve giving total

line strength as a function of the number of absorbing atoms, which in various forms continues to be widely used up to the present day.

In 1940 the last commercial plane to leave Europe for America, before the war finally closed in, carried copies of the *Photometric Atlas of the Solar Spectrum* by Minnaert and his two pupils, J. Houtgast and G. F. W. Mulders, a publication which is still a standard work of reference. After the war he and his staff used the atlas for the *Preliminary Photometric Catalogue of Fraunhofer Lines, λ 3164- λ 8770*, followed in 1966 by *The Solar Spectrum 2935 Å-8770 Å*, in cooperation with C. E. Moore and J. Houtgast. He also published two authoritative and very useful articles in Kuiper's series on the solar system, in Volume I on *The Photosphere* (1953) and in Volume III on *Photometry of the Moon* (1961). Mention should be made also of his last book, *Practical Work in Elementary Astronomy* (1969), a first introduction to many of the practical techniques of optical astronomy which characteristically relies on demonstrations with only the simplest equipment.

A brief summary of his technical publications gives a very inadequate picture of one who, by his enthusiasm and idealism, his modesty and sincerity, his good humour and extraordinarily wide range of interests and abilities, made a profound impression on everyone he met. He was a natural and tireless teacher of astronomy and an equally persistent opponent of popular belief in astrology. Perhaps his best known publication is *De Natuurkunde van 't Vrije Veld*, of which Volume I—known in English translation under the title

Light and Colour in the Open Air—is a masterpiece of popular science describing the optical phenomena associated with meteorology. He was an excellent linguist and revealed a wide and appreciative acquaintance with European literature in *Dichters Over Sterren*, a multilingual anthology of poetry dealing with stars and astronomy. He was a talented musician and at one time he possessed a remarkable collection of musical instruments which he later donated to the University of Utrecht.

He was on the staff of the Utrecht Physical Laboratory and later the Observatory for altogether 44 years; he was director of the Observatory and professor of astronomy from 1937 until his retirement in 1963, and more than any other man was responsible for building up the strong school of astronomy which still flourishes there.

He was a strong supporter of international causes, especially of the International Astronomical Union, and served as chairman of several of its commissions. For many years he was exiled from his native Belgium because of his open advocacy of the Flemish movement and during the Second World War he was one of about a hundred Dutch intellectuals who were imprisoned as hostages by the Nazis under daily threat of execution. Grateful witnesses have testified at first hand to how much he did during this time, by organizing talks and lectures, to preserve the morale and even the sanity of his fellow prisoners.

Among the many honours he received were the Gold Medal of the Royal Astronomical Society and the Bruce Medal of the Astronomical Society of the Pacific.

Announcements

University News

Professor A. J. Youngson and Professor Denys Hay have been appointed vice-principals of the University of Edinburgh, in succession to Professor J. W. Crofton and Professor D. Talbot Rice respectively.

Dr R. Goldsmith, University of Nottingham, has been appointed to the chair of physiology at Chelsea College, University of London.

Mr George King, chief scientist of Standard Telecommunication Laboratories Limited, has been appointed visiting professor in telecommunications in the University of Surrey.

Appointments

Dr J. P. Wild has been appointed chief of the CSIRO Division of Radiophysics, in succession to Dr E. G. Bowen.

Dr J. Morton Boyd has been appointed director of the Nature Conservancy in Scotland, in succession to Dr W. J. Egging.

Dr V. Armstrong, New Zealand, has been appointed chairman of the executive council of the Commonwealth Agricultural Bureaux, in succession to Mr W. G. Alexander, and Mr E. S. Kapotwe, Zambia, has been appointed vice-chairman.

Miscellaneous

Sir Martin Ryle has been awarded the

Faraday medal of the Institution of Electrical Engineers for his contribution to the design and engineering of new types of aperture synthesis aerials and associated equipment.

Applications are invited by the trustees of the Lady Tata Memorial Trust for fellowships and scholarships for research on leukaemia, particularly studies of the leukaemogenic viruses in mammals, the epidemiology and natural history of leukaemia and the immunogenic aspects. The awards are available to qualified investigators of any nationality, working in their own institutions or abroad. Further information can be obtained from the Secretary of the (European) Scientific Advisory Committee, Lady Tata Memorial Trust, Chester Beatty Research Institute, Fulham Road, London SW3.

British Diary

Monday, January 18

Biological Control Systems (6.30 p.m.) Mr P. M. H. Rack and Mr I. C. Whitfield, Institution of Electrical Engineers, at the University, Liverpool.

Scanning Microscopy (7 p.m.) Institution of Electrical Engineers, at the Wheat-sheaf Hotel, Peterborough.

The Examination and Teaching of "The Engineer in Society" (6 p.m. discussion) Institution of Mechanical Engineers, at 1 Birdcage Walk, London SW1.

The Mechanism of Genetic Recombination (5.30 p.m.) Dr H. L. K. Whitehouse, in the Anatomy Theatre, University College London, Gower Street, London WC1.

Tuesday, January 19

ADSEL—Selectively Addressed Secondary Radar (6 p.m.) Mr C. Ulyatt, Institution of Electronic and Radio Engineers, at 9 Bedford Square, London WC1.

Colour Television (6.30 p.m.) Mr B. J. Rodgers, Institution of Electrical Engineers, at Worthing College of Further Education, Worthing.

Distribution Practice in Malaysia (5.45 p.m.) Mr J. Sharples, Institution of Electrical Engineers, in the Renold Building, UMIST, Manchester.

Motorways and the Rural Environment (5.30 p.m.) Mr G. D. Spearing and Mr M. R. Porter, Institution of Civil Engineers, at Great George Street, London SW1.

The Legal Requirements Relating to Pressure Vessel Design (6 p.m. discussion) Institution of Mechanical Engineers, at 1 Birdcage Walk, London SW1.

Ultrasonics (7.45 p.m.) Mr R. L. Barton, Institution of Electrical Engineers, at the Castle Hotel, Taunton.

Wednesday, January 20

A Review of Liquid Cooling of High Temperature Gas Turbine Rotor Blades (6 p.m.) Mr F. J. Bayley and Professor B. W. Martin, Institution of Mechanical Engineers, at 1 Birdcage Walk, London SW1.

Linear Integrated Circuits (6.30 p.m.) Mr P. J. Jefferson, Institution of Electronic and Radio Engineers, in the Physics Lecture Theatre, The University, Leicester.

On-Line Analysis (4 p.m.) Society for Analytical Chemistry, at the North Staffordshire Polytechnic, Stoke-on-Trent.

Television Standards Conversion (7.30 p.m.) Institution of Electronic and Radio Engineers, in the Physics Depart-

ment, Robert Gordon's Institute of Technology, St Andrews Street, Aberdeen.

The Application of Some Solid-Gas and Liquid-Gas Reactions of Analytical Chemistry (6.30 p.m.) Professor R. Belcher, Society for Analytical Chemistry, in the Department of Chemistry, South Road, Durham University.

The Black Arrow X 3 Spacecraft (6.30 p.m.) Mr H. J. H. Sketch, Institution of Electrical Engineers, at Savoy Place, London WC2.

The Care and Restoration of Books and Manuscripts (6 p.m.) Mr A. D. Baynes-Cope, Society for the Bibliography of Natural History, in the Men's Staff Common Room, University College London, Gower Street, London WC1.

The Development of the Printing Press (2.30 p.m.) Mr James C. Moran, Royal Society of Arts, at John Adam Street, London WC2.

Thursday, January 21

Aspects of Current Chopping (6.30 p.m.) Mr G. Spence, Institution of Electrical Engineers, at Sunderland Polytechnic, Chester Road, Sunderland.

Special Problems of Paints and Mastics with reference to Building Techniques (7 p.m.) Mr E. L. French, Oil and Colour Chemists' Association, at The Beech Tree Hotel, Beaconsfield, Bucks.

The Analysis of the Newer Metals (3.45 p.m.) Mr W. T. Elwell, Society for Analytical Chemistry, jointly with the Heriot-Watt University Chemical Society, at the Heriot-Watt University, Edinburgh.

The Establishment of a Modern Aluminium Reduction Industry in Anglesey (7 p.m.) Mr E. J. Stephens, Liverpool Metallurgical Society, in the Department of Metallurgy and Minerals Science, The University, Liverpool 3.

The Future of Water-Thinnable Coatings (7 p.m.) Mr A. J. Becalick, Oil and Colour Chemists' Association, at the British Rail School of Transport, London Road, Derby.

The Role of Serum Antibodies in Malarial Immunity (7.30 p.m. symposium) Royal Society of Tropical Medicine and Hygiene, at Manson House, 26 Portland Place, London W1.

The Role of the World Bank in Agricultural Development (2.30 p.m.) Dr O. T. W. Price, Fertiliser Society, at the Geological Society, Burlington House, Piccadilly, London W1.

The State of the Art in Computer Aided Mechanical Engineering Design (6 p.m. discussion) Institution of Mechanical Engineers, jointly with the Institution of Electrical Engineers and the Institute of Measurement and Control, at 1 Birdcage Walk, London SW1.

Friday, January 22

Flash Photolysis—ESR Studies of Photo-Oxidation of Chlorophyll (1 p.m.) Dr B. J. Hales, Royal Institution, Photochemistry Discussion Group, at 21 Albemarle Street, London W1.

The Magnetic Butterfly (9 p.m.) Professor E. R. Laithwaite, Royal Institution, at 21 Albemarle Street, London W1.

Saturday, January 23

Homo Sapiens, New Light on Man's Origins (3.30 p.m.) Dr Michael H. Day, Inner London Education Authority, at the Horniman Museum, London Road, Forest Hill, London SE23.

Monday, January 25

Changes and the Future in Electrical Engineering (7.30 p.m.) Mr S. Z. de Ferranti, Institution of Electrical Engineers, at the Free Trade Hall, Manchester. (Faraday Lecture.)

Computer Graphics and the Electrical Engineer (6.30 p.m.) Mr M. Clayton and Mr D. W. Davis, Institution of Electrical Engineers, at Liverpool Polytechnic, Byrom Street, Liverpool.

Concorde Electronics (6.30 p.m.) Mr H. Hill, Institution of Electrical Engineers, at Salisbury and South Wiltshire College of Further Education, Salisbury.

Reports and Publications

not included in the monthly Books Supplement

Great Britain and Ireland

The Royal Society. Report of Council for the year ended 31 August 1970. Pp. 101 (London: The Royal Society, 1970.) [3011

Cotton Research Corporation. Progress Reports from Experiment Stations, Season 1968/1969. Swaziland. Pp. 13. 2s. 6d. Zambia. Pp. 40. 2s. 6d. (London: Cotton Research Corporation, 1970.) [3011

Chelsea College of Science and Technology, University of London. Annual Report 1969/1970. Pp. 72. (London: Chelsea College of Science and Technology, 1970.) [3011

Dairy Products. (Proceedings of a Seminar organized by the Agricultural Institute, Republic of Ireland, 21–22 May, 1969.) Edited by T. R. Ashton, E. L. Crossley, F. O'Connor and A. C. O'Sullivan. Pp. 59. (London: Society of Dairy Technology, 1970.) 26s. 3d. [3011

Cranfield Institute of Technology. Annual Report 1969/1970. Pp. 59. (Cranfield, Bedford: Cranfield Institute of Technology, 1970.) [3011

Measurement of Moisture in Solids: a Survey Based on Scientific and Technical Literature. By P. J. Geary. Pp. 89. (Chislehurst, Kent: Sira Institute, South Hill, 1970.) Sira members 150s.; Non-members 210s. [3011

The British Council. Annual Report 1969/1970. Pp. 112. (London: British Council, 1970.) [3011

Morganite Special Carbons for Mechanical Engineering. Pp. 24. (London: Morganite Carbon, Ltd., 1970.) *gratis*. [112]

Papers from the Department of Geology, University of Glasgow, Vol. XXVIII. 53 papers. (Glasgow: The University, 1970.) [112]

Ministry of Technology. Ministry of Defence. Official Definition of Coral 66. (Prepared by the Inter-Establishment Committee on Computer Applications as a Language Standard for Military Programming.) Pp. vii+57. (London: H.M.S.O., 1970.) 10s. net. [212]

Philosophical Transactions of the Royal Society of London. A: Mathematical and Physical Sciences. Vol. 268, No. 1189, (26 November, 1970): Asymptotic Solutions for High-Frequency Trapped Wave Propagation. By R. Smith. Pp. 289-324. 17s.; \$2.20. Vol. 268, No. 1190, (26 November 1970): Stokes Multipliers for the Orr-Sommerfeld Equation. By W. D. Lakin and W. H. Reid. Pp. 325-349. 13s. \$1.70. (London: The Royal Society, 1970.) [212]

The British Cancer Council. People and Cancer; and the Problem of Relevance in Cancer Research. (Two Meetings). Pp. 112. (London: The British Cancer Council, 1970.) 10s. [212]

Forestry Commission. Forest Record No. 73: Ploughing Practice in the Forestry Commission. By G. G. M. Taylor. Pp. 44. 4s. (20p) net. Fiftieth Annual Report and Accounts of the Forestry Commission for the year ended 31st March 1970, together with the Comptroller and Auditor General's Report on the Accounts. Pp. 92. 14s. (70p) net. (London: HMSO, 1970.) [212]

Periodical Publications in the National Reference Library of Science and Invention. Part 3: List of current titles in the Holborn Division. Fourth edition. Pp. 383. (London: Trustees of the British Museum, 1970.) 35s. [212]

Science Museum. Science Library Bibliographical Series, No. 796: Some References to Petroleum Microbiology, 1965-1970. Pp. 8. (London: Science Museum, 1970.) [212]

The Nuffield Provincial Hospitals Trust. Eighth Report covering activities during the years 1967-70 and including a cumulative classification of Research and Development supported by the Trust 1940/70. Pp. 112. (London: The Nuffield Provincial Hospitals Trust, 1970.) [312]

Psychological Medicine, Vol. 1, No. 1, November 1969. (A Journal for Research in Psychiatry and the Allied Sciences.) Pp. 1-100. Annual Subscription: 75s., UK and Republic of Ireland; 84s. (USA \$11, Canada \$12) in all countries overseas. Single issues: Inland 25s. Abroad 30s. USA \$3.50. (London: British Medical Association; Boston, Mass.: *British Medical Journal*, 1172 Commonwealth Avenue, 1970.) [412]

Is Apprenticeship Outdated? By E. J. Singer and I. D. Macdonald. Pp. 36. (London: Institute of Personal Management, 1970.) 12s. (60p) [412]

Department of Education and Science. Statistics of Education 1969. Vol. 1: Schools. Pp. xvii+99. (London: HMSO, 1970.) 34s. net. [412]

Other Countries

Canada: Department of Energy, Mines and Resources. Geological Survey of Canada. Paper 69-45: A Catalogue of Canadian Minerals. By R. J. Traill. Pp. 649. (Ottawa: Queen's Printer, 1970.) \$5. [3011]

International Atomic Energy Agency. Technical Report Series, No. 118: Reference Methods for Marine Radioactivity Studies. Pp. 284. 181 schillings; 58s. 4d.; \$7. Technical Report Series No. 119: Manual on Mutation Breeding. (A Joint Undertaking by the Food and Agriculture Organization of the United Nations and the International Atomic Energy Agency.) Pp. 237. 155 schillings; 50s.; \$6. (Vienna: IAEA, 1970.) [3011]

Background Study for the Science Council of Canada. Special Study No. 11: Background to Invention—A Summary of Views on the Canadian Patent System and on Industrial Research and Development Activities in Canada. By Andrew H. Wilson. Pp. 77. (Ottawa: Queen's Printer, 1970.) \$1.50. [3011]

Instituto de Investigacao Cientifica de Mocambique. Novos Taxa Entomologicos. No. 77: Descriptions of Three New Species of Miltogramminae (Diptera: Sarcophagidae) from the Ethiopian Geographical Region. By F. Zumpt. Pp. 8. No. 78: Contribuicao para o Estudo dos Dinastineos Africanos. IX: Dinastineos da Costa do Marfim. Por M. C. Ferreira. Pp. 18. (Lourenco Marques: Instituto de Investigacao Cientifica de Mocambique, 1970.) [112]

National Radiation Laboratory, Christchurch, New Zealand. Quarterly Report (January-March 1970), Environmental Radioactivity in New Zealand and Results of Extended Monitoring of Fallout from French Nuclear Tests in the Pacific for Samples Processed up to 27 July. Pp. 29. (Christchurch: National Radiation Laboratory, 1970.) [112]

Annals of the Transvaal Museum, Vol. 26, No. 11 (30 September 1970): A Revision of the Genus *Ischnodemus* Fieber in the Ethiopian Region (Hemiptera: Lygaeidae, Blissinae). By James A. Slater and Jane E. Harrington. Pp. 211-275—plates 23 and 24. (Pretoria: Transvaal Museum, 1970.) [212]

Deutsches Hydrographisches Institut. Jahresbericht 1969. Pp. 110. (Hamburg: Deutsche Hydrographisches Institut, 1970.) [212]

Instituto de Investigacao de Mocambique Novos Taxa Entomologicos. No. 80: A New Species of *Stygionympha* Van Son from Namaqualand (Lepidoptera, Rhopalocera, Satyrinae). By K. M. Pennington. Pp. 5. No. 81: *Phumosia spangleri*, a New Species from Uganda, and Re-Description of *Phumosia lesnei* (Séguy) from Mozambique (Diptera: Sarcophagidae, Calliphoridae). By F. Zumpt. Pp. 7. (Lourenco Marques: Instituto de Investigacao Cientifica de Mocambique, 1970.) [212]

Wattle Research Institute, (South African Wattle Growers' Union; South African Timber Growers' Association; University of Natal; State Department of Forestry)—Report for 1969/1970 (Twenty-third year). Pp. 56. (Pietermaritzburg: Wattle Research Institute, University of Natal, 1970.) [312]

Geological Survey of Western Australia. 1: 250,000 Geological Series—Explanatory Notes. Ashton, Western Australia: Sheet SE/52-9 International Index. Compiled by G. M. Derrick. Pp. 18. Kalgoorlie, Western Australia: Sheet SH/51-9 International Index. Compiled by M. J. B. Kriewaldt. Pp. 17. Mount Elizabeth, Western Australia: Sheet SE 52/1 International Index. Compiled by H. G. Roberts and W. J. Perry. Pp. 16. Naretha, Western Australia: Sheet SH/51-16 International Index. Compiled by D. C. Lowry. Pp. 12. Wyloo, Western Australia: Sheet SF/50-10 International Index. Compiled by J. L. Daniels. Pp. 18. Annual Report for the year 1969. Pp. 72. (Perth: Geological Survey of Western Australia, 1969 and 1970.) [312]

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